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## CONTENTS

Factors Which Influence Recovery from Acute Anuria *J A Stirman* 1
*Benign Adrenal Cysts J G Steeluff* 9
Roentgenological Appearance of Normal Adrenal Glands *R H Harrison, III and L C Doubleday* 16
Partial Nephrectomy for Echinococcus Cyst *P H Aschner and Elias Gechman* 23
Longevity Following Nephrectomy *A E Goldstein* 31
Influence of Furadantin Treatment on Stone Growth Experimental Urolithiasis XI *G H Miller W H Chapman L Seibulis and C W Vermeulen* 42
Diagnosis of Early Renal Carcinoma by Exfoliative Cytology *S H Bassow* 47
Biopsy of Lower Ureter *B A Smith, Jr* 53
Bilateral Periureteritis Plastica *J H Hejtmancik and M A Magid* 57
Complete Valve of Ureter Congenital Urethral Valves *R R Roberts* 62
Study of Motor Paralytic Bladder in Poliomyelitis *B G Clarke* 66
Lower Urinary Tract in Treated Neurosyphilis *Morton Bogash Jose Figueroa Colon J J Pegues P R Leberman and J J Murphy* 70
Perineal Sigmoidostomy in Cases of Total Cystectomy *O G Stonington and Ben Eiseman* 74
Chronic Urethritis *W A Grimes J J Cordonnier and C F Humphreys* 83
Construction of Perineal Urethra by Split Thickness Skin Graft *A B Peyton and J W Headstream* 90
Paraurethral Cyst Within Corpus Cavernosum Urethrae *C G Weller* 94
Cytochemical Observations on Corpora Amylacea of Human Prostate Gland *A R Seaman* 99
Prostatic Corpora Amylacea *G C Prather and David Skinner* 107
Factors that Expedite Transurethral Prostatic Resection *P A Bleakney and J P Packard* 115
Treatment of Chronic Urinary Tract Infection in Children with Nitrofurantoin *Matthew Marshall, Jr and S H Johnson III* 123
New Ureteral Clamp *R K Arnell* 129

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*Annual Meeting, American Urological Association, Hotel William Penn*
*Pittsburgh, Pennsylvania, May 6–9, 1957*

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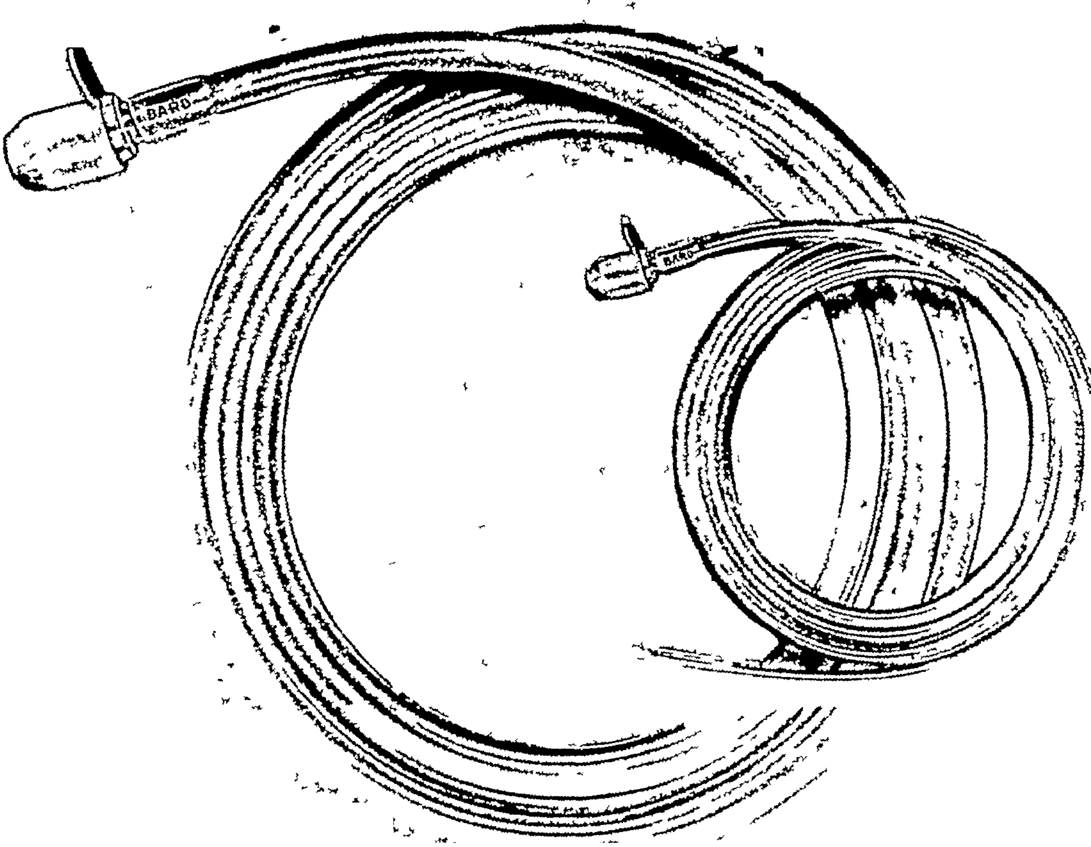

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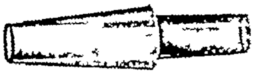

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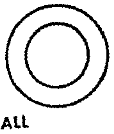

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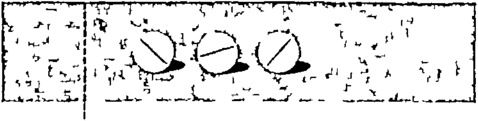

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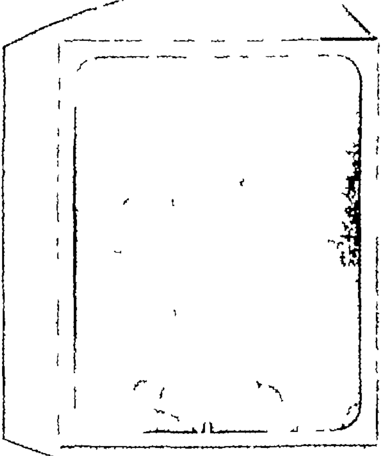

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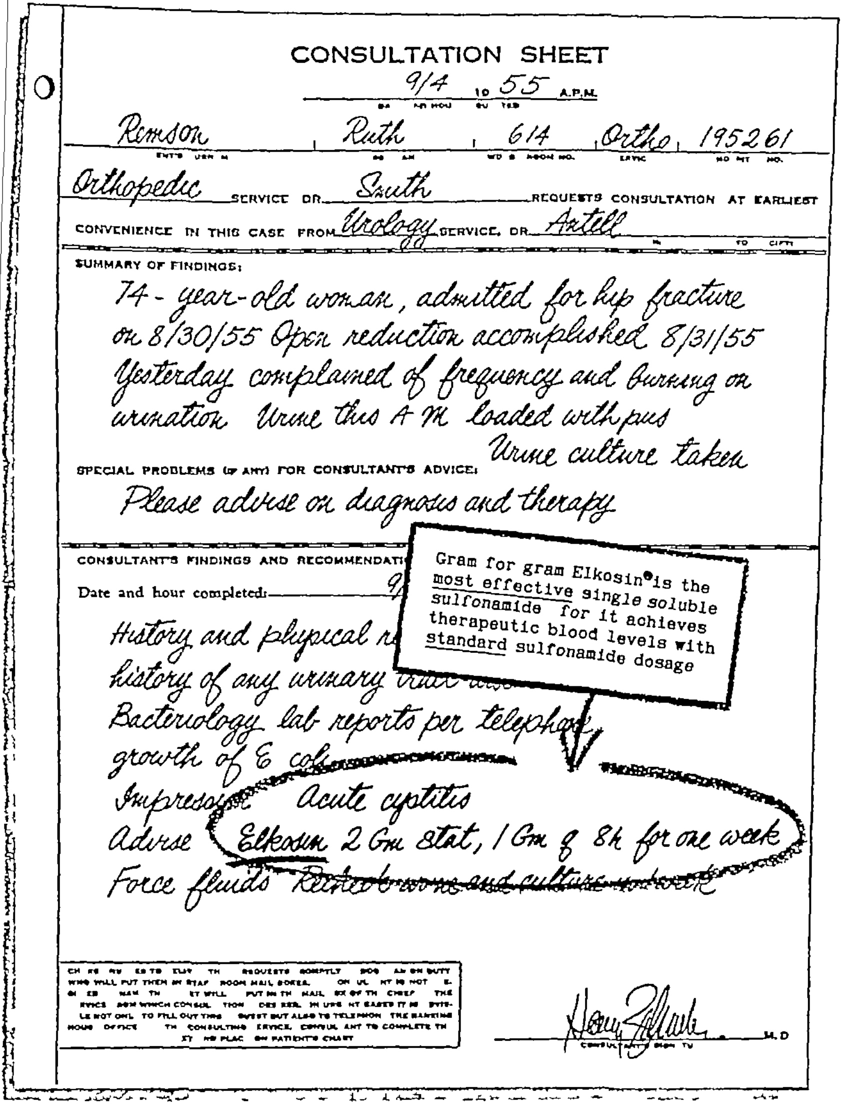

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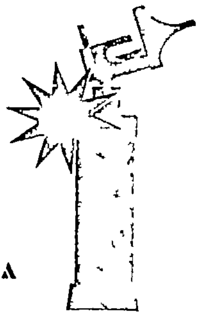

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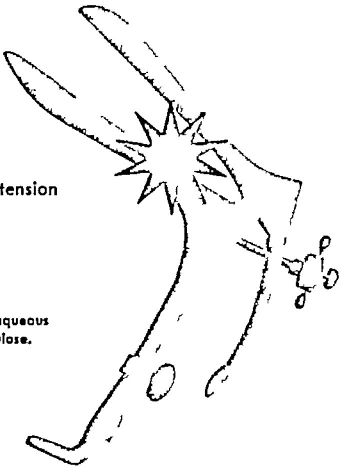

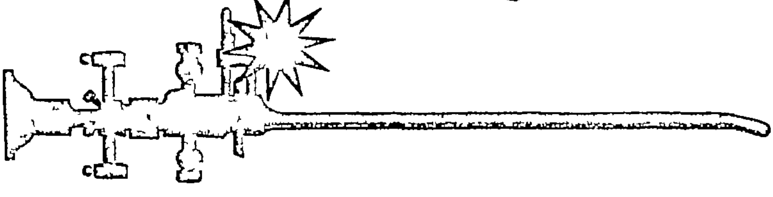

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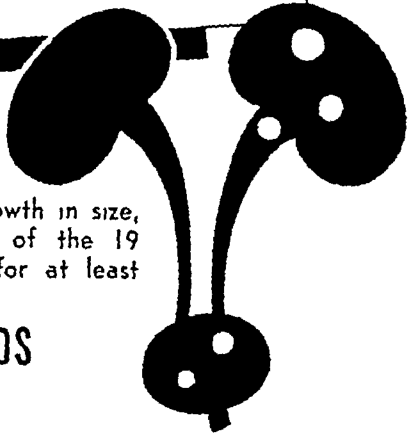

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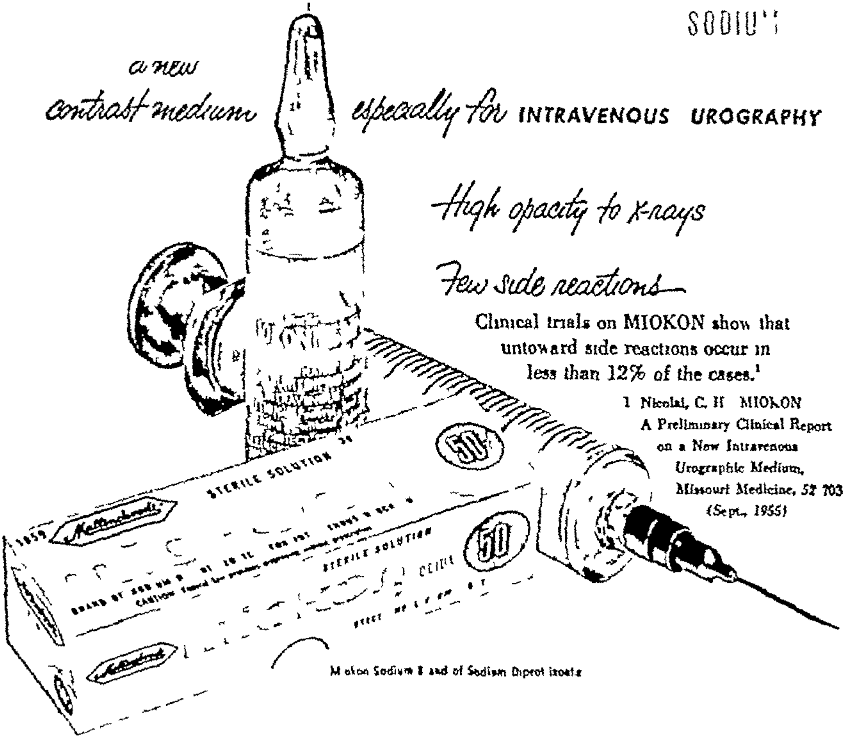

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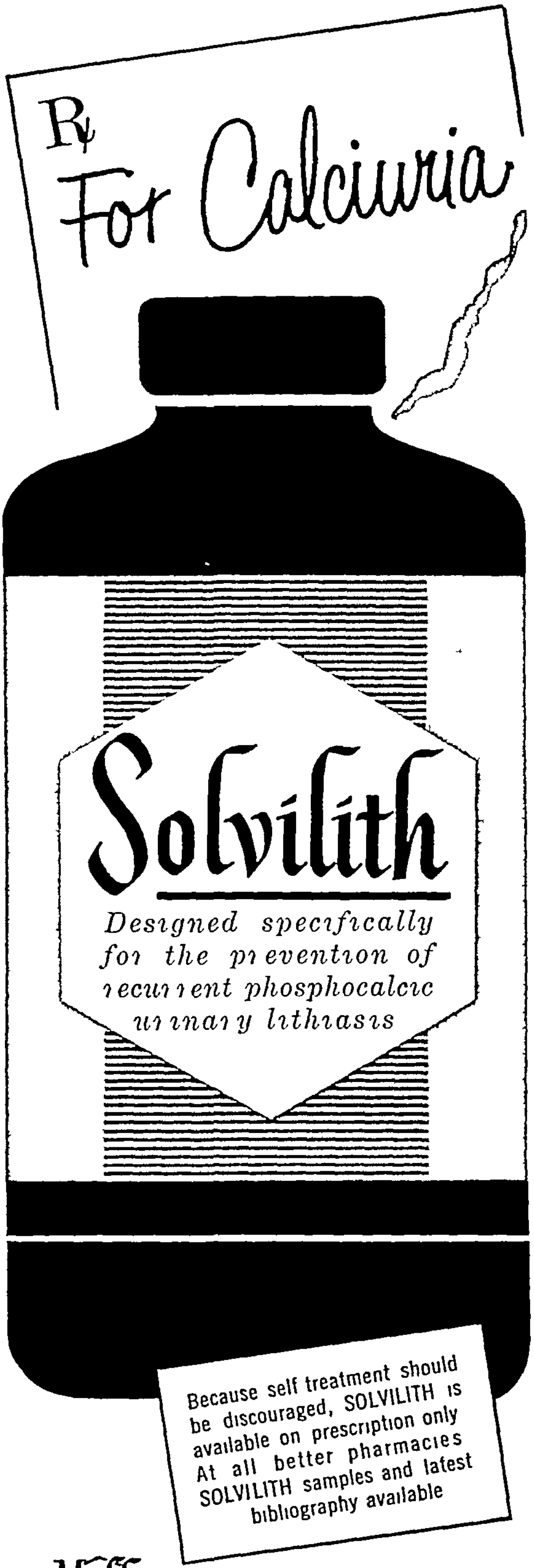
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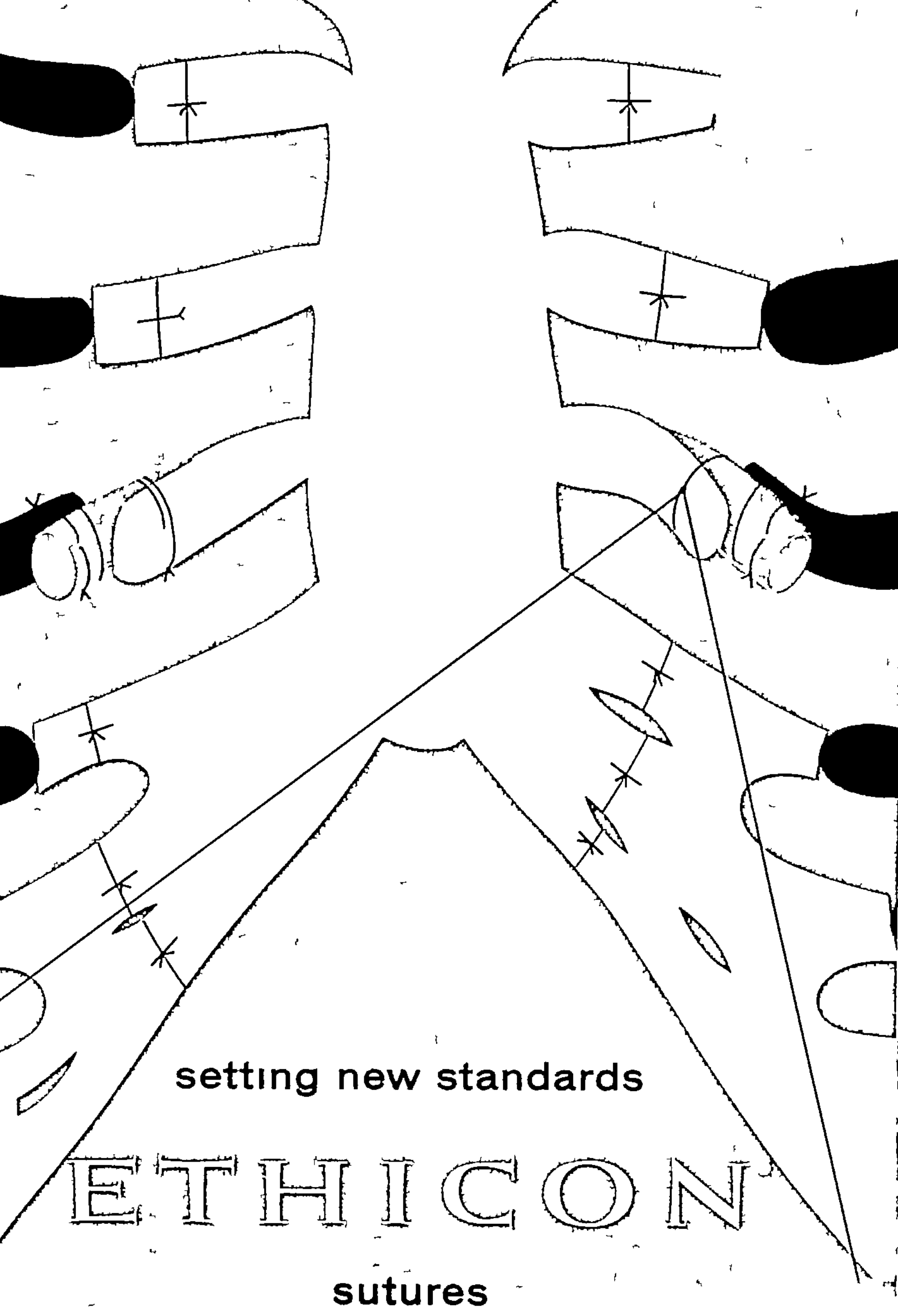
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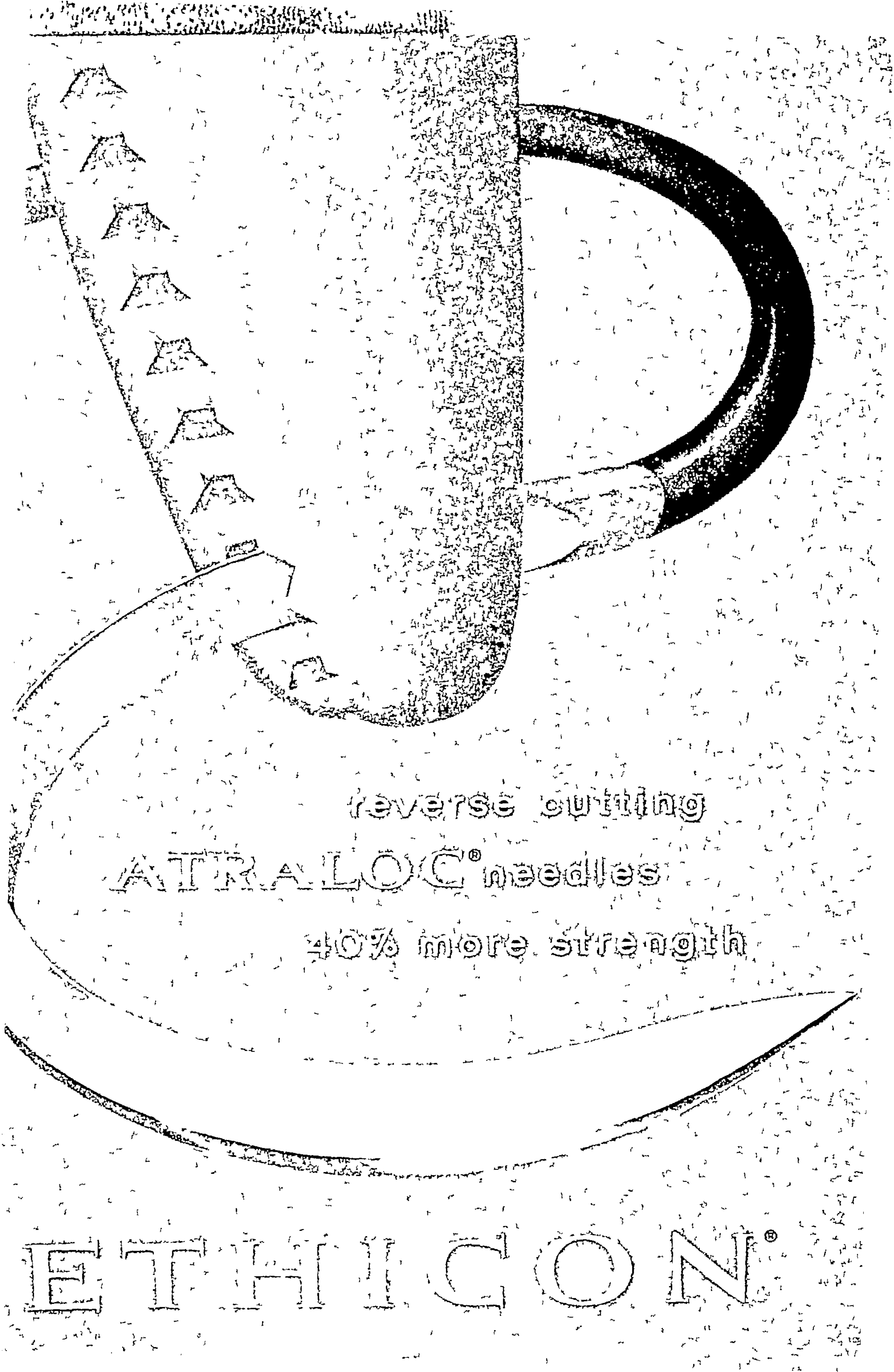
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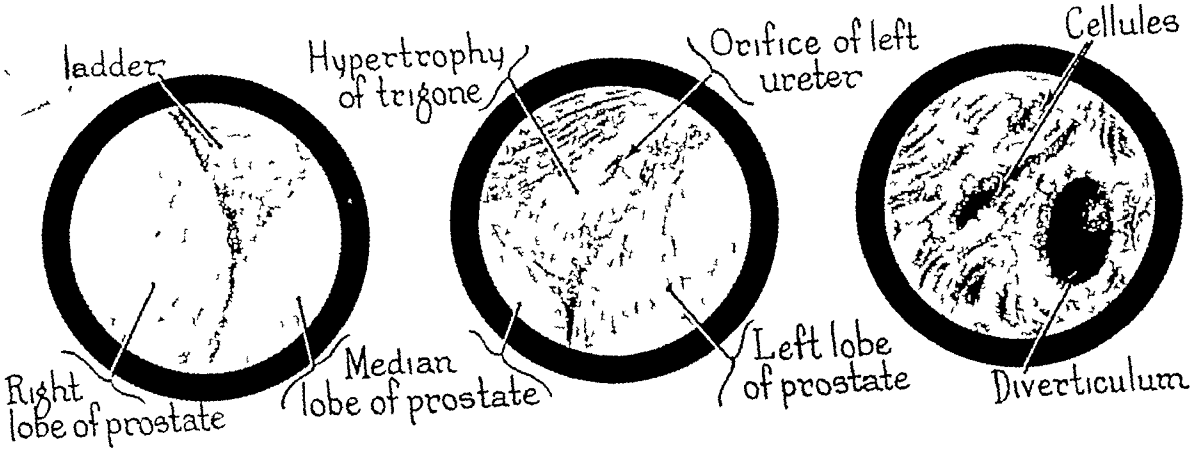
ladder
Hypertrophy of trigone
Orifice of left ureter
Cellules
Right lobe of prostate
Median lobe of prostate
Left lobe of prostate
Diverticulum

The Journal of Urology
Vol. 76 No 1 July 1956
*Printed in U.S A*

# FACTORS WHICH INFLUENCE RECOVERY FROM ACUTE ANURIA

JERRY A STIRMAN

*From the Department of Surgery University of Texas, Southwestern Medical School, Dallas Texas*

Acute cessation of urine flow may follow either changes in the volume or concentration of the fluid delivered to a normal kidney or result from renal damage The differentiation of the etiologic site of disease which is evidenced by a single symptom—oliguria—must be made if a physiologic approach to therapy be applied This report presents an approach to the dissection of factors of etiologic and functional significance in the oliguric patient, the correlative aspects of treatment, and the discussion of management of acute renal failure

An etiologic classification of acute anuria is presented in table 1 The discussion which follows specifically omits acute anuria due to urinary tract obstruction and high output renal failure seen following release of an obstruction [1]

## ACUTE FUNCTIONAL ANURIA

*Shock due to whole blood loss* The effects of hemorrhagic shock on renal function cannot be categorically stated, for all types of shock do not produce the same changes in renal function The two major types of shock encountered in surgical practice are those associated with 1) a decreased blood volume-oligemic shock and 2) a normal volume vasoparalytic shock The general effects of oligemic peripheral circulatory failure on renal function are more directly related to the decrease in cardiac output than to the changes in blood pressure [2, 3] This is borne out by the normal renal clearance measurements obtained during hypotension associated with spinal anesthesia and hexamethonium bromide [4, 5] This vasoparalytic shock is usually associated with a normal cardiac output If oligemic shock due either to the loss of whole blood, or to the loss of salt water is properly and adequately treated early enough, then the depressed renal function is readily reversible If not so treated, or if there is the superimposition of a hemolytic transfusion reaction, or if there are associated fluid and electrolyte abnormalities renal function may not be readily reversed to normal The specific treatment of the shock state is a factor frequently overlooked in the assessment of a response of the patient to the treatment

---

Read at annual meeting South Central Section of American Urological Association San Antonio, Texas October 17-19 1955

Supported in part by Air Force Contract AF 18 (600) 1261

[1] Wilson Ben Reisman, D D and Moyer C A Fluid balance in the urological patient Disturbances in renal regulation of the excretion of water and sodium salts following decompression of the urinary bladder J Urol 66 805-815 1951

[2] Corcoran A C and Page I H Effects of hypotension due to hemorrhage and of blood transfusion on renal function in dogs J Exp Med 78 205 1943

[3] Lauson H D Bradley S E and Cournand A The renal circulation in shock J Clin Invest., 23 381, 1944

[4] Corcoran A C, Taylor R D and Page I H Circulatory responses to spinal and caudal anesthesia in hypertension Relation to the effect of sympathectomy II Effect on renal function Am Heart J 36 226-240 1948

[5] Churchill Davidson H C Wylie W D Miles B E and de Wardener H E The effects of adrenaline, noradrenaline and methedrine on the renal circulation during anesthesia Lancet 2 803-805 1951

TABLE 1

---

I Functional Anuria of Oliguria
  A) Shock associated with
    1) Whole blood loss
    2) Extracellular fluid volume loss
    3) Mixed losses of ECF and blood
  B) Extracellular fluid volume deficit without shock
  C) Water excess
  D) Water deficit
II Organic Anuria or Oliguria
  A) Protracted functional anuria or oliguria
  B) Transfusion reaction
  C) Toxic nephrosis, chemical nephrosis
  D) Bacteremia or septicemia with shock
  E) Acute nephritis or acute exacerbation of chronic nephritis
III Obstructive Uropathies

---

What, then, are the responses of renal function in oligemic shock to appropriate and inappropriate treatment?

1) Blood loss shock, if treated by the administration of blood, is associated with the return of the clinical evidences of shock to normal and the renal clearance measurements towards, but not completely to, normal The general vasoconstriction attending shock is participated in by the kidney, however, there is a proportionately greater increment in renal resistance than in peripheral resistance[3]

2) Hemorrhagic shock treated by the administration of a salt solution alleviates the shock state and increases renal clearance measurements towards normal[6] This obtains as long as the shock state is controlled by the saline infusion The improvement in renal function is maintained by the subsequent infusion of whole blood

3) Plasma expander infusion improves the shock state The restoration of renal function occurs essentially to the same extent and duration as treatment with a similar volume of a salt solution[6]

4) The administration of a vasopressor agent in hemorrhagic shock induces a rise in blood pressure If the loss of circulating volume is minor, then improvement in renal clearance measurements is noted If, however, blood volume loss is severe, then no appreciable increment in renal function occurs If over correction of the blood pressure is induced, renal function decreases further[7]

5) Blood loss shock treated by the administration of water may not be associated with increase in renal function nor restoration of vital signs One of the characteristics of renal function change in peripheral circulatory failure is a decrease in the ability to excrete a water load The load administered by improper treatment produces water intoxication and its attendant effects on renal function

---

[6] Raiz L Dextran and oxypolygelatin as plasma volume expanders Renal excretion and effects on renal function J Lab & Clin Med , 40 880–890, 1952

Moyer, J , Handley, C A and Huggins, R A The effect of adrenergic blockade and norepinephrine on renal and cardiovascular hemodynamics following hemorrhage Circulation Res , 2 441–447, 1954

*Shock due to extracellular fluid volume loss* The depression of renal function from this type of oligemic shock is similar to that associated with hemorrhagic shock and demands specific therapy

The administration of a balanced salt solution* in this type of shock effects a rapid return of renal function toward normal This is indicated clearly in a case report which follows

Case 1 A 48-year-old laborer was admitted to the hospital suffering from acute appendicitis and generalized peritonitis An appendectomy was performed On the fifth postoperative day nausea, abdominal distension, and intractable diarrhea developed Thirty hours after the onset of the diarrhea the blood pressure fell to 40/0, the pulse rate rose to 120 He became restless and began to sweat profusely The urinary output had been 10 ml for the preceding 18 hours The blood urea nitrogen was 60 mg per cent The physical examination demonstrated decreased skin turgor, collapsed veins and the other signs of peripheral circulatory failure The administration of 4 liters of a balanced salt solution within 2 hours brought the blood pressure to 100/60, the pulse rate to 100, and the urine output to 50 ml Subsequently, 5 liters of a balanced salt solution were administered in order to completely restore the patient to normal

The foregoing case report illustrates the rapidity of response of the cardiovascular system to the infusion of an adequate volume of a balanced salt solution Reliance on whole blood therapy in such a state is not only unnecessary but may be dangerous For even though the administration of whole blood may return the vital signs toward normal, there is not restoration of renal function to normal An experimental comparison of salt water infusion and whole blood infusion as to their capacities to effect complete physiologic recovery from shock due to extracellular fluid volume loss was performed

Acute extracellular fluid volume deficit with shock was induced in dogs by the intraperitoneal dialysis of 10 per cent glucose in distilled water in the volume of 150 cc/kg The animal was treated with compatible whole blood on one occasion and a balanced salt solution after a second depletion experiment (table 2) Whole blood restored the blood pressure to normal yet failed to produce complete restoration of the glomerular filtration rate Twenty four hours later the blood urea nitrogen had increased Restoration of renal function to normal ensued following the administration of a balanced salt solution after a similar depletion experiment The blood urea nitrogen did not rise after 24 hours

*Shock due to mixed losses of extracellular fluid and blood* Shock states incident to the losses of both extracellular fluid and whole blood require the repletion of both Since physicians and especially surgeons are conditioned to replace whole blood losses promptly, the less obvious losses of extracellular fluid are frequently not appreciated nor replaced This failure to replace extracellular fluid may permit inadequate renal blood flow to persist beyond the time that the blood pressure in the arm has returned to normal The following case report is given as an example of this phenomenon

Case 2 A 52 year-old man was admitted for treatment of a carcinoma of the

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* A balanced salt solution is one that has ionic composition and concentration similar to that of extracellular fluid for example Hartmann s solution

TABLE 2

| | Control | Depletion | Blood | Depletion | Salt |
|---|---|---|---|---|---|
| BP (mm Hg) | 133 | 80 | 106 | 80 | 120 |
| G F R (cc/min ) | 57 0 | 14 7 | 26 6 | 16 1 | 40 4 |
| Blood urea (mg %) | 22 4 | 18 4 | 31 4 | 44 6 | 61 6 |
| 24 hours later | | | 44 4 | | 33 0 |

stomach A total gastrectomy was performed The operative procedure was long (8 hours) and tedious The estimated blood loss was 1500 cc of blood During the entire procedure the patient sweated profusely The last 2 hours of the procedure were characterized by a slow but progressive fall in blood pressure, and a rising pulse rate, which were treated by the administration of whole blood with improvement of the vital signs The total blood administered was 3 liters The postoperative hemoglobin concentration was 17 gm per cent, the preoperative was 12 5 gm per cent During the operative procedure there was an estimated salt water loss of between 3 and 4 liters, which was not replaced, and probably accounted for the gradual decline in the vital signs Although the vital signs responded to the administration of whole blood, renal function was not improved The following morning there was evidence of a mild extracellular fluid volume deficit, the 24-hour urinary output was 150 ml The correction of the extracellular volume deficit at this time did not restore urine flow, and it was apparent that he was then suffering from an acute organic anuria

This patient and several others have demonstrated the deleterious effect on renal function that the administration of excessive quantities of whole blood may have when given in the presence of an extracellular fluid volume deficit The simultaneous administration of a balanced salt solution and whole blood would likely have promoted prompt improvement in renal function and might have prevented the additional injury to the kidney which culminated in severe organic damage

*Extracellular fluid volume deficit without shock* The overall loss of electrolytes and water in the same proportions as they exist in the extracellular fluid results in an extracellular fluid volume deficit The clinical features of this deficit are characteristic somnolence, loss of skin elasticity, wrinkled but moist tongue, tachycardia, soft veins, oliguria or anuria, and a rise in blood urea nitrogen The concentrations of the plasma electrolytes are not necessarily altered in this deficit [8] In acute deficits the hemoglobin and hematocrit values may be high, if the deficit is of long duration these concentrations may be normal or low The administration of a balanced salt solution in adequate amounts restores the individual to normal Such a result may obtain even though the oliguria may have been present for 24–48 hours

*Water excess* Inappropriate treatment of the aforementioned condition with a non-salt-containing fluid tends to improve volume at the expense of decreasing extracellular electrolyte concentration The resultant effect is water intoxication

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[8] Moyer, C A Fluid Balance Chicago Year Book, 1952

The typical symptoms are headache, blurring of vision, muscular twitchings, excessive salivation and lacrimation, increased intracranial pressure, a rising blood pressure, a decreased pulse rate, at times, diarrhea or vomiting, decrease in urine flow rate and rising blood urea nitrogen Coma, convulsions, and papille dema occur as the relative water load increases The practice of forcing fluids" to persons with an elevated blood urea is fraught with the risk of inducing a water excess and jeopardizing renal function further, especially if organic disease of the kidney exists, or if the individual is old The administration of hypertonic salt solution corrects the electrolyte dilution

*Water deficit* Water deficit incurred by restriction of water intake is associated with a decrease in urine flow but decreases in renal function have not consistently been measured A rise in blood urea nitrogen usually occurs The clinical symptoms of thirst, rising body temperature, hallucinations delusions, maniacal behavior, dry mucous membranes and elevated electrolyte concentrations indicate a deficit of water The administration of normal saline usually intensifies the clinical symptoms and increases the osmotic load demanding excretion Water given by mouth or glucose in water by vein effects recovery

The early recognition of a functional anuria, the institution of appropriate and adequate therapy usually result in rapid restoration of renal function However, if the condition producing the functional anuria is not recognized early, or if improper and inadequate therapy is given, a functional anuria may be converted into an organic anuria

### ACUTE ORGANIC ANURIA

Once the diagnosis of an organic anuria has been made the principles of therapy are in general independent of the precipitating factors The primary differences in therapeutic approach depend upon the previous state of fluid and electrolyte balance and the presence of a simultaneous major injury and/or infection

The general principles of management of the patient who has an organic anuria are 1) no exogenous potassium, 2) no exogenous protein, 3) restriction of intake of water and sodium, 4) at least 100 gm of carbohydrate daily, 5) prevention of and/or active treatment of abscess, hematomas, and necrotic tissue

The most common cause of death in acute renal failure is hyperkalemia The rapidity of development of hyperkalemia is related to the rate of tissue break down (catabolic index)[9] extracellular electrolyte dilution, increasing acidosis, and the level of serum calcium In bilaterally nephrectomized rabbits a rise in serum potassium may occur in association with a falling serum sodium produced by exogenous water load[10] Since potassium and calcium are physiologic antagonists the low serum calcium which usually obtains in acute renal failure tends to augment the cardiotoxic effect of hyperkalemia[11] The greater the tissue breakdown the more rapidly potassium is liberated The demonstration of ex tracellular entry of potassium when acidosis is induced in dogs would indicate that perhaps the severity of the acidosis may play a part in the development of hyperkalemia [12]

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[9] Merrill J P and Swann R C The clinical course of acute renal failure Medicine **32**, 215–292 1953

[10] Muirhead, E E Personal communication

[11] Teschan Paul E et al Post traumatic renal insufficiency in military casualties I Clinical characteristics II Management use of an artificial kidney, prognosis Am J Med 18 172–198 1955

Measures which may control hyperkalemia are the administration of calcium, the dilution of potassium, the improvement of acidosis, and improvement of electrolyte dilution by the administration of hypertonic sodium lactate, the metabolic incorporation of potassium by administration of glucose and insulin, and the administration of digitalis The effectiveness of these measures is short lived for no external loss of potassium is promoted The potassium exchange resins when administered orally or rectally in doses of 50 to 100 gm daily usually will reduce the serum potassium [13] Artificial hemodialysis is the most effective means of reducing an acute elevation of serum potassium, this procedure also corrects the acidosis, electrolyte dilution, and serum calcium concentration

The administration of exogenous protein increases the nitrogenous and potassium load During the anuric or oliguric phase and until renal function recovers the administration of protein is contraindicated

One hundred grams of carbohydrate given daily exerts a protein-sparing action Additional amounts of glucose are difficult to administer owing to the need for rigid restriction of water

The restriction of water and electrolytes and the prevention of electrolytes and the prevention of electrolyte dilution are closely related

The most common fluid and electrolyte aberration seen is dilution of extracellular electrolytes This is directly related to the amount of water given, and the amount of water derived from endogenous metabolism All losses except sweating and insensible loss are subject to direct measurement and therefore, can be replaced quantitatively according to volume, composition and concentration Endogenous sources of water depend upon the rate of tissue breakdown An average of about 450 ml/day of endogenous water has been reported in anuric states [13] If tissue breakdown is extremely rapid, as in massive injury, then available water from catabolism is much greater than 450 ml per day Consequently, in replacing insensible losses, the rate of tissue breakdown must be taken into consideration Fluid replacement therapy in an individual with a slow rate of tissue breakdown* should consist of replacement of the measurable losses (urine, suction drainage) plus about 250 ml of water/day The guide to therapy is the serum sodium concentration If this remains at about a normal level then an appropriate quantity of water is being administered provided a weight loss of about 0 5 to 1 0 pound per day obtains Changes in the serum level of sodium may be corrected by giving additional water or by the abstention from water Individuals in whom the catabolic rate is excessive should receive no free water other than that which is measurably lost The level of serum sodium is similarly used as a guide In patients who are conscious this severe restriction of water produces intense thirst and dry mucous membranes These features are probably related to the rise in total osmolarity of the body fluids incident to the retention of nitrogenous products These signs in the anuric patient do not necessarily indicate the need for additional water, for if water is given to allay thirst electrolyte dilution will follow which may delay the onset of diuresis[14] If water intoxication occurs after the onset of diuresis there will be a fall in urine output and a rise of blood urea nitrogen

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[12] Keating, R E, Weichselbaum, T E, Alanis, M, Margraf, H W and Elman, R The movement of potassium during experimental acidosis and alkalosis in the nephrectomized dog Surg, Gynec & Obst, 96 323, 1953

[13] Elkington, J R and Danowski, T S The Body Fluids Baltimore Williams and Wilkins, 1955

* The note of tissue breakdown can be estimated by the accretion of blood urea nitrogen—a rise of 10–20 mg per cent per day represents a slow rate of protein catabolism

Abscesses, hematomas, and necrotic tissue produce excessive quantities of nitrogenous products and potassium[11] Early and vigorous surgical treatment is necessary to minimize these effects

The major differences in the management of renal failure which is attended by massive trauma, as apposed to renal failure without trauma, mav be summarized

1) Removal of potassium by means of exchange resins is usually ineffective since potassium release is very rapid Most of these patients are unable to tolerate the resin by mouth Rectal administration has been far less efficacious in our experience than oral administration

2) The water freed by endogenous catabolism may be in excess of 500 ml /day consequently, no exogenous water need by supplied except in combination with electrolytes to replace lost fluid which can be measured Salt water losses from the wounds are common

3) Severe acidosis appears early

4) The indications for hemodialysis appear early in many of these patients

The indications for artificial hemodialysis are

1) Uncontrolled hyperkalemia

2) The need for correction of water intoxication when the administration of hypertonic sodium salts might provoke cardiovascular overload This situation exists in patients who have an extracellular fluid volume excess

3) A severe progressive acidosis

4) Deterioration of clinical state This is usually preceeded by a change in mental state and muscular twitchings

5) Gross overloads producing uncontrolled pulmonary edema

6) Occasionally a fulminant rise in blood urea nitrogen

The expected results of artificial hemodialysis are a return of plasma electrolyte values to normal at least a 50 per cent reduction in blood urea nitrogen, improvement in mental state, and relief of nausea, vomiting, and abdominal distension The only contraindication to artificial hemodialysis is a bleeding tendency There has been little morbidity related to artificial hemodialysis in our experience

The principles of artificial dialysis and comparative efficiency of the Kolff and Skeggs Leonards' artificial kidney have been previously reported[15] The chief advantages of the Skeggs-Leonards artificial kidney are ultrafiltration can be accomplished if desired, there is a fixed volume of blood in the machine at any time, the unit is portable

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[14] Hamburger J and Mathe J Ciba Foundation Symposium on the Kidney Boston Little, Brown and Co , 1954

[15] Kolff A J and Higgins C C Dialysis in the treatment of uremia Artificial kidney J Urol 72 1082 1954

## SUMMARY

The causes of acute anuria other than obstruction are functional and organic The return of urine flow may be expected to follow early, specific, and adequate therapy of functional anuria Inappropriate treatment may convert a functional anuria into an organic anuria The various types of functional anuria and the response to different types of treatment have been discussed Administration of whole blood to correct the shock associated with an extracellular fluid volume deficit does not restore renal function even though the vital signs improve

The therapy of an organic anuria depends upon the rate of tissue catabolism Rapid catabolism produces early hyperkalemia, progressive acidosis, and dilution of the extracellular electrolytes The rigid restriction of exogenous water is particularly important in rapidly progressive acute renal failure Artificial hemodialysis is only an important adjunct to treatment

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# BENIGN ADRENAL CYSTS

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Benign cyst of the adrenal gland is an uncommon disease which is rarely diagnosed preoperatively Parker, in 1951, found nineteen cases in the American literature Ellis, Dawe, and Clagett, in 1952, reviewed 12 cases of their own in which the lesion was removed at operation Most of the cases reported before 1952 were accidental findings at necropsy Wahl reported nine cases in 13,996 autopsies All of these were accidental findings According to Rabson and Zimmerman and also Zuckner, most of the cysts found at necropsy have been small and produced no symptoms, but these cysts do become large enough to present problems in diagnosis Parker's case presented a palpable tumor as did ten of the twelve cases reported by Ellis

The etiology of these cysts is not well understood Terrier and Lecene, in 1906, classified adrenal cysts as parasitic, true glandular retention cysts, cystic adenomas, serous or lymphangiomatous cysts and pseudo cysts Reimann and Guyton state that the mechanism by which adrenal cysts are formed does not coincide with the manner in which true retention or inclusion cysts are developed They believe adrenal cysts result usually from ectasia of pre-existing vessels or cystic degeneration of hematomas or adenomas, and are therefore better called pseudo cysts

Ellis states that the adrenal glands do not contain acini with a central lumen which can become distended with secretion Therefore, he believes that, with the exception of embryonic cysts, it is unlikely that glandular or retention cysts occur in the adrenal gland He further states that while cystic adenomas may occur, satisfactory reports of cases are difficult to find Parasitic cysts are exceedingly rare (Barnett) Reimann and Guyton state that the gross appearance of adrenal cysts varies as does the pathogenesis Those cysts resulting from ectasia of lymph channels consist of numerous locules and contain clear, milky fluid The hematocysts have irregularly pigmented walls which may contain islands of calcareous material Cysts of this type may contain bloody or reddish brown fluid and portions of adrenal gland may be stretched out over the surface of the cyst

Ellis classified the twelve cases he studied as serous cysts and pseudo cysts The pseudo cysts in his series resulted from hemorrhage and necrosis in a benign or malignant tumor or from cystic resolution of a hematoma in the absence of neoplasm

Adrenal cysts do occur in infants and children Campbell reported seven cases in children under five years of age Several cases have been reported in which the condition was associated with congenital adrenal insufficiency LeCompte collected 52 cases of adrenal hemorrhage in newborn infants, of which thirty-three were bilateral He believed that if the infants survived, these might become encapsulated and form hematomas

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Read at annual meeting, South Central Section of American Urological Association San Antonio Texas, October 17–19 1955

The reported cases requiring diagnosis and treatment have all been in adults In none of these cases has there been any evidence of endocrine deficiency The diagnosis can not be made on the presenting symptoms Pain in the upper abdomen or in the region of the cyst, bloating, belching, nausea, vomiting, and constipation are frequent complaints Gastrointestinal symptoms apparently result from pressure of the cyst on the gastrointestinal tract Pyelographic studies make possible the diagnosis Calcification in the cyst walls is common and will show on the film However, it is also seen in pancreatic and dermoid cysts In most of the cases reviewed there was downward displacement of the kidney on the involved side Soft tissue mass above the kidney was frequently seen Presacral or perirenal air injection was not done in any cases reported but would certainly be valuable

## CASE REPORTS

I wish to report two cases encountered this year

*Case 1* A 40-year-old married woman was admitted to the hospital February 1, 1955, complaining of pain in the right flank and abdomen, nausea, vomiting, and discomfort when she attempted to stand erect She was more comfortable bending over and to the right Her symptoms began 24 hours before admission and gradually increased in severity Six weeks earlier she had had a similar attack, which was less severe and lasted for 3 hours

On admission to the hospital her temperature was 99 8F The blood pressure was 110/74 No physical abnormalities were found other than tenderness in the right flank and abdomen The abdomen was flat There was voluntary muscle guard over the right side There was pain in the right flank on pressure and also pain on pressure over the lower abdomen The patient was menstruating Pelvic examination revealed no abnormality *

The white blood count was 9,800 There were 72 segmented neutrophilic cells and 6 stab cells, 2 monocytes, 1 eosinophil, and 19 lymphocytes The red blood count was 4,200,000, and the hemoglobin was 82 per cent A catheterized urine specimen revealed no abnormalities

A diagnosis of acute retrocecal appendicitis was made Laparotomy was done a few hours after admission and a normal appendix was removed The surgeon explored the abdomen manually through a right rectus incision and found a cystic mass involving the upper pole of the right kidney I saw the patient 5 days later Her course had been uneventful following the appendectomy There was no history of any significant illness in the past There had been no change in her normal menstrual cycle Her three pregnancies had been entirely uneventful and had ended in normal term deliveries There was no history of injury There were no symptoms suggestive of endocrine deficiency

On examination the abdomen was flat and soft and there was no palpable mass or tenderness Neither kidney was palpable

Excretory urography revealed an oval shaped, soft tissue mass lying above the superior pole of the right kidney (fig 1) The mass measured 8 by 5 cm It

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* Personal communication (February, May 1955) from Dr Curtis H Epps

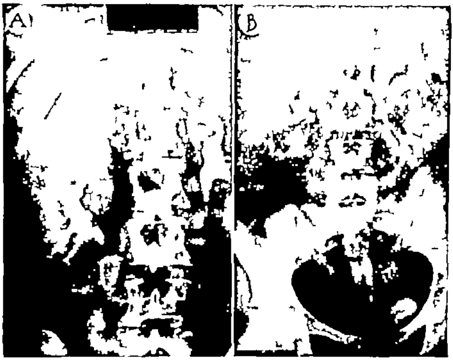

FIG 1 Case 1 *A* excretory urogram, 15-minute film demonstrating slight downward displacement of right kidney with soft tissue tumor mass noted above it Calcification in suprarenal area on both sides is also seen *B* excretory urogram 10 minute film demonstrating soft tissue tumor mass above right kidney which is displaced downward

appeared distinct from the kidney although in close apposition to it Irregular calcific densities were noted in both suprarenal areas There was slight downward displacement of the right kidney from its normal position Both kidneys functioned normally to concentrate the contrast medium There was no deformity of the calyces or pelvis of the right kidney Retrograde pyelograms done the following day revealed normal kidney pelves and ureters bilaterally with slight downward displacement of the right kidney A routine chest film revealed no evidence of disease of bone or soft tissue

On the eighth day after appendectomy, the patient was operated upon through a flank incision The twelfth rib was removed A cystic mass 7 cm in diameter was found It was attached to the upper pole of the right kidney only by fatty tissue The tumor was mobilized easily and removed A portion of the adrenal gland was left in place

The gross specimen consisted of a round, fibrous-walled, purple cyst (fig 2) Compressed adrenal gland tissue appeared spread over the surface of the cyst at two points One calcareous plaque was palpable On section, thin chocolate colored fluid escaped The cyst lining was covered with dark brown fibrin and was in most part perfectly smooth The wall measured 1 to 2 mm in thickness A yellowish calcium plaque 1 cm wide was found at one point in the lining of the cyst

Sections through the wall of the cyst showed the outer surface covered with a thin layer of adrenal cortical tissue This tissue was atrophic showing an irregular infiltration of lymphocytes and an irregular distribution of lipoids The lining was smooth and composed of hyalinized connective tissue that was fairly acellular except for a few phagocytes containing hemosiderin The content of the cyst was made up of degenerated blood This appeared to be an old hematoma undergoing liquefaction and reabsorption The histologic diagnosis was encysted hematoma of the adrenal gland

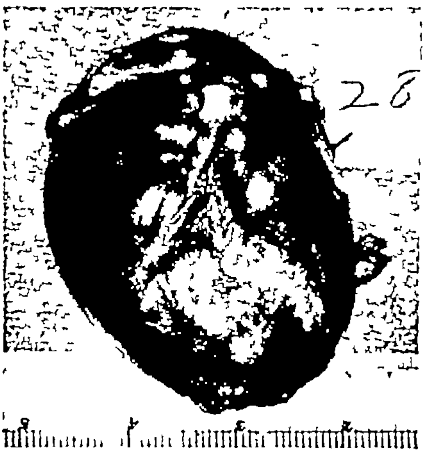

FIG 2 Case 1 Right adrenal hematocyst measuring 8 by 5 cm

The patient made an uneventful recovery and has had no further symptoms

The history of this case would suggest that the patient may well have had a hemorrhage into a cyst at the time of her first attack of pain 6 weeks prior to operation Calcification noted on the film in both suprarenal areas suggests that she may have had some adrenal infection at a previous time with possible hemorrhage and cyst formation

*Case 2* A small, thin, healthy-appearing woman 39 years of age was admitted to the hospital March 31, 1955, for a hemorrhoidectomy She requested consultation with a urologist because of soreness in the right back and flank which she said had been present many years She had been told in May 1952 that this was due to nephroptosis In January 1952 she consulted a physician complaining that for years she had had soreness in the right flank and back with pain which occasionally radiated into her right thigh and down to her right foot She stated that she had been able to feel a lump in her right side for several years * During these years she had had recurrent dyspepsia with gas, belching, and abdominal distention

On physical examination her blood pressure was 126/80 No physical abnormality was noted The abdomen was flat and soft The right kidney was readily palpable and appeared normal in size and shape There was slight tenderness in the right upper quadrant of the abdomen There was no costovertebral angle tenderness She was convalescent from a hemorrhoidectomy

Cystoscopic examination revealed no abnormality of the lower urinary tract Pyelograms revealed a downward displacement of the kidney (fig 3, *A*) A soft tissue mass, which measured 9 cm in its greatest diameter, lay at the superior pole of the right kidney At the medial aspect of the mass, there was an area of multiple, linear, calcified opacities Bilateral pyeloureterograms revealed normal pelvic and calyceal structure bilaterally The right kidney was displaced downward Oblique projections suggested that the soft tissue mass was retroperitoneal The relationship of the mass to the kidney did not change in either the erect or Trendelenburg position (fig 3, *B* and *C*) A cholecystogram revealed a normally

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* Personal communication (February, May 1955) from Dr Curtis H Epps

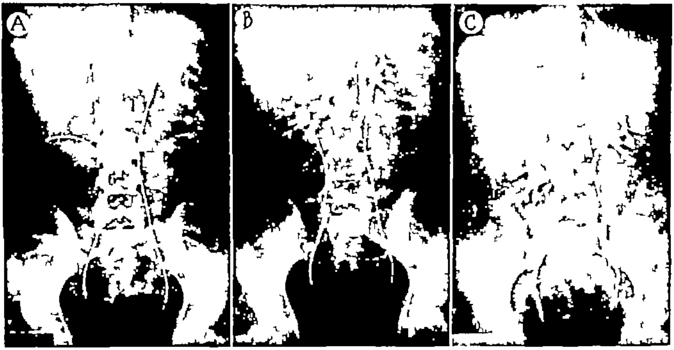

FIG 3 Case 2 *A* retrograde pyelogram demonstrating displacement of right kidney downward by soft tissue mass and calcification which proved to be within cyst wall *B* pyelogram taken with patient in Trendelenburg position demonstrating downward displacement of kidney in absence of distortion of calyceal outline *C* retrograde pyelogram with patient in erect position demonstrating soft tissue tumor mass above right kidney

functioning gallbladder and demonstrated the linear calcific shadows to lie outside the gallbladder area Gastrointestinal studies revealed no abnormality The excretory pyelogram done in 1952 was reviewed The radiologist on that occasion described the calcific shadows and suggested they might represent a calcified hemangioma of the liver The soft tissue mass was present on these films but not so well outlined as on the later film

A diagnosis of adrenal cyst was made and surgical removal was advised The patient returned to the hospital for operation April 24, 1955 No essential change in her physical condition was found at that time The VDRL was negative The hemoglobin was 13 2 The hematocrit was 41 There were 8,700 white cells with 17 stab cells, 35 segmented cells, one eosinophil, 41 lymphocytes, and 6 monocytes present The catheterized urine revealed no abnormality

Operation was done through a right flank incision which was made over the eleventh rib since the twelfth rib was vestigial. A soft, fibrous walled cyst approximately 9 cm in diameter was found lying above the right kidney It was not attached to the kidney It was dissected without difficulty The only firm attachment the cyst had was to the adrenal gland It was excised leaving the major portion of the adrenal gland in place

The gross specimen measured 9 by 5 cm (fig 4) It was smooth, lobulated grayish white in color and irregular plaques of yellowish adrenal cortical tissue were seen stretched out over portions of the cyst wall On section, a cloudy white fluid escaped The cyst wall was thin and fibrous The lining was smooth except at one pole and there a few fibrous trabeculae were found which contained calcified plaques These areas were related to the remaining adrenal cortical tissue

Microscopically, the cyst fluid contained a few red blood cells and numerous small refractive globules which apparently accounted for the white, cloudy appearance of the fluid They were not soluble in ether Chemical analysis of the

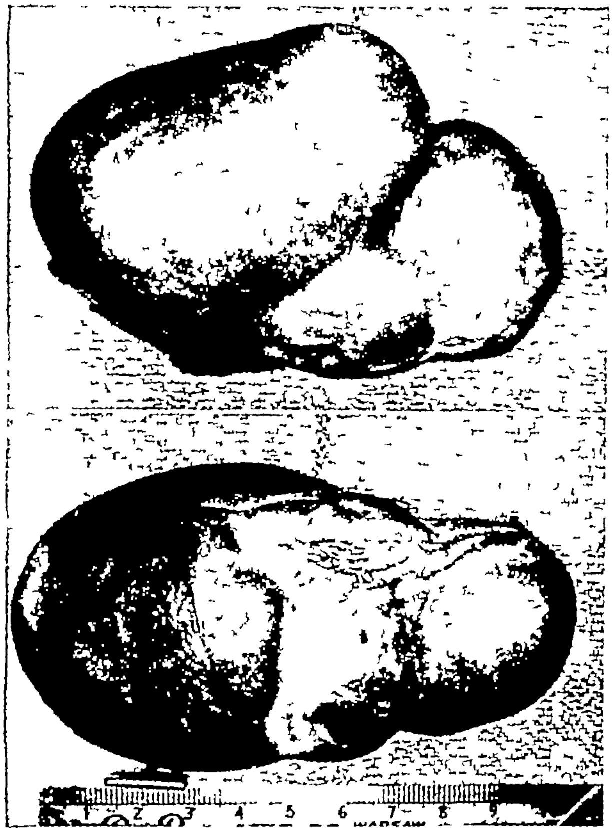

FIG 4 Case 2 *A*, benign adrenal cyst measuring 9 by 5 cm *B*, benign adrenal cyst demonstrating compressed adrenal gland tissue over cyst wall

cyst fluid was reported as chlorides 111 4 mEq/l, sodium 146 mEq/l, potassium 6 2 mEq/l, urea nitrogen 12 2 mg , cholesterol 318 mg , total proteins 6 0 mg , albumin 3 25 mg , globulin 3 35 mg , AG ratio 0 97 to 1 0 The pathologist concluded that the cyst's contents were probably of lymphatic origin

Section of the cyst wall showed it to be lined with a thin layer of endothelial cells backed by a layer of fairly acellular dense collagen In some areas, compressed remnants of cortical and medullary tissue extended into the fibrous trabeculae However, remnants of medullary tissue were usually in this location Some of the fibrous trabeculae showed linings replaced with calcium deposits Diagnosis Adrenal cyst, probably of lymphatic origin

The patient had an uneventful recovery following her surgery and has remained asymptomatic since that time

## SUMMARY

The etiology of adrenal cyst is not established but most of those removed at operation appear to be pseudo cysts rather than glandular retention cysts

Two cases of benign adrenal cyst removed at operation are reported Both of these may be considered pseudo cysts

Pain in the region of the cyst and symptoms related to the gastrointestinal tract have been present in the cases reported

These cysts do not appear to cause endocrine disease

Pyelographic studies have been the most important diagnostic procedure

Perirenal or presacral air injection would be of value in the diagnosis of this condition

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# ROENTGENOLOGICAL APPEARANCE OF NORMAL ADRENAL GLANDS

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Subsequent to Carelli's description of perirenal air insufflation and supplemented by Rivas' presacral air technique, many articles have appeared in the world literature largely dealing with the diagnosis of pathological conditions of the kidney and the adrenal

In many instances, in good quality plain films of the abdomen, it is possible to discern the adrenal areas and determine whether an adrenal cortical tumor of clinical significance is likely to be present or not without resorting to air studies

When a patient presents with clinical evidence of so-called Cushing's syndrome and air studies have been done, it may be difficult to state whether or not there is roentgen evidence of adrenal hyperplasia when a definite cortical tumor is not demonstrated in the films

Here an attempt is made to determine roentgenologically the size and appearance of normal adrenal glands in order to establish more definite criteria which may assist the clinician in making a diagnosis A review of the literature on the various techniques and results of air insufflation is not included

## ANATOMY

Gray's textbook of anatomy describes the right adrenal as having the appearance of a "cocked hat" and the left adrenal as being semilunar or crescent shaped (fig 1) It should be noted that the upper lateral portion of the right adrenal bears a direct relationship to the bare area of the liver laterally and the inferior vena cava medially and anteriorly The left adrenal is located superiorly and medially to the upper pole of the kidney, inferiorly, the anterior surface lies in relation to the splenic vessels and the tail of the pancreas These adjacent structures apparently account for the difference in their anatomical characteristics

Rivas clinically emphasized that Gerota's fascia is deficient inferiorly which allows gas to pass inside it and diffuse around the kidney and adrenal as well as passing externally to it (figs 2 and 3)

## TECHNIQUE

Presacral retroperitoneal air studies were performed on 50 charity patients admitted to Jefferson Davis Hospital for nonendocrine disorders In none was active retroperitoneal disease anticipated Room air was used in all, the amount varied from 200 cc in an infant to 2,000 cc in a 100 kg female patient, the average being 1,000 cc per 65 kg individual The youngest patient was 4 weeks old, the oldest 85 years old In 13, additional urological studies were performed simultaneously, namely, retrograde pyelography in five, excretory urography

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Read at annual meeting, South Central Section of American Urological Association, San Antonio, Texas, October 17–19, 1955

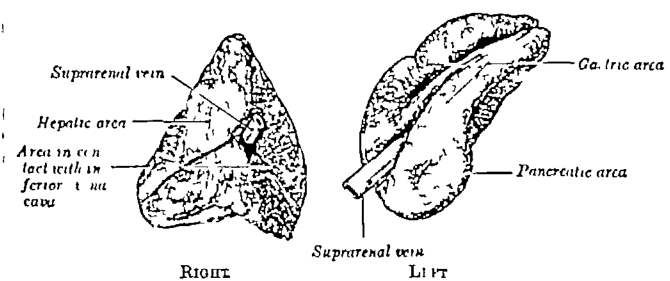


FIG 1 Anterior aspect of normal adrenal glands From Gray's Anatomy of Human Body

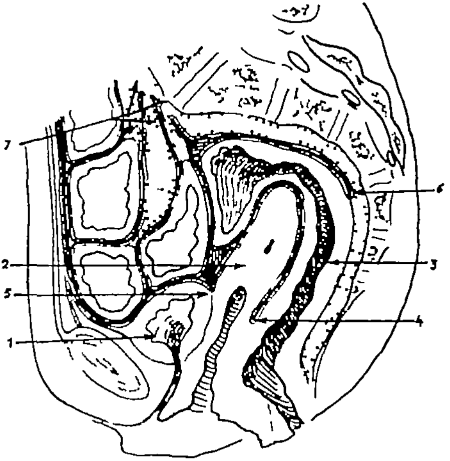


FIG 2 Retrorectal and pelvic fascial anatomy Hatched area represents path of air ascent After Rivas *1* Bladder *2* uterus *3* rectum *4* rectovaginal sac *5* vesicovaginal sac *6*, sacroretrorectal sac *7* mesenteric roots

in four, and aortography in four In all instances the air was injected observing the usual precautions with the patient in the lithotomy position

Radiographs were made in the anteroposterior supine position with the target film distance being 36 inches Additional films were made during the first several hours, then daily until the films were no longer of diagnostic value Thereafter, films were made twice a week until the air had been absorbed

## COMPLICATIONS

Following injection, all patients complained of lower abdominal fullness initially, probably a result of the air dissecting upward and anteriorly It usually persisted for a few hours and occasionally up to 24 or 36 hours In 3 cases shoulder pain and/or paroxysms of coughing developed, probably indicating diaphragmatic irritation Subcutaneous emphysema developed in 25, lasting from a few hours up to 48 hours Two patients required opiates and/or sedation in the first 24 hours for relief of abdominal discomfort There was no morbidity after 48 hours nor any deaths

Although in this series no injection had to be discontinued before the decided amount of air was given, it is mandatory to stop injection if a patient complains of chest pain alone, a symptom of mediastinal emphysema During injection, should a patient suddenly become cyanotic and develop chest pain, nausea, irregular respiration, fall in blood pressure and tachycardia, gas embolus is to be suspected Immediately the patient should be placed with his right side up and supportive measures begun Placing the patient in this position relieves the "air-trap" in the outflow tract of the right ventricle

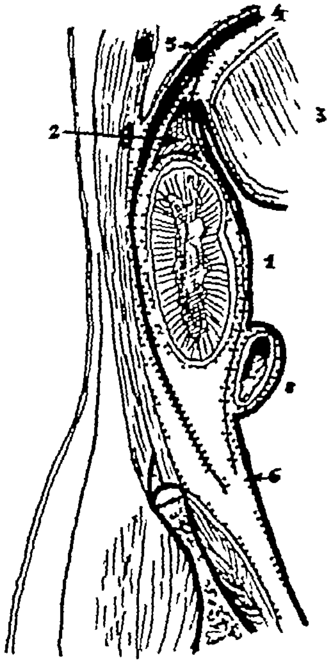


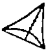
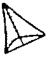
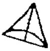
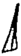
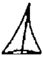
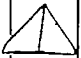
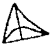
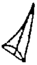
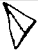
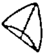
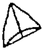
FIG 3 Demonstration of inferior defect in Gerota's fascia After Rivas *1*, Kidney, *2*, suprarenal capsule, *3*, liver, *4*, diaphragm, *5*, pleura, *6*, peritoneum, *7*, renal fascia with inferior outlet, *8*, retroperitoneal colon

Steinbach and Smith reviewed some 3,500 cases from at least 17 major institutions, including 350 of their own in which 2 deaths from gas embolus are reported

## RESULTS

Although the majority of cases showed fairly good distribution of air by 30 minutes, the best films most constantly were in 24 hours In 13 of the cases, both adrenals were adequately demonstrated for our calculations In 31, at least one adrenal was visualized Although some air persisted in one patient for 3 weeks, the average number of days until complete absorption was twelve

TABLE 1 *Roentgenographic measurement of adrenal glands*

| CASE | CASE No | SHAPE* |  | RIGHT ADRENAL |  |  | LEFT ADRENAL |  |  |
|---|---|---|---|---|---|---|---|---|---|
|  |  | Right | Left | Base | Height | Area | Base | Height | Area |
|  |  |  |  | cm | cm | cm | cm | cm | cm |
| E.T 43 C.F<br>AT 9399<br>99546 | 20 | | | 2.4 | 1.5 | 1.2 | 2.4 | 1.9 | 2.0 |
| D.R 27 W F<br>CF 2140<br>99598 | 23 |  |  | 3.2 | 2.1 | 2.4 | 2.9 | 2.5 | 2.5 |
| J.M. 12 C M<br>XX 2009<br>77356 | 24 |  | | 3.3 | 2.0 | 2.4 | 2.8 | 1.6 | 1.5 |
| B.S. 27 C.F<br>CF 2380<br>99753 | 28 |  | | 1.0 | 4.0 | 1.1 | 3.0 | 2.0 | 2.9 |
| W.W 19 C.M.<br>CF 2327<br>78181 | 29 |  |  | 2.6 | 3.0 | 3.2 | 5.0 | 3.5 | 8.2 |
| J.M. 25 C.M.<br>CF 1083<br>98959 | 30 | | | 3.0 | 1.5 | 1.5 | 3.0 | 1.5 | 1.5 |
| B.S. 45 W.M.<br>C F 2224<br>96209 | 33 | |  | 2.8 | 1.4 | 1.5 | 3.2 | 1.6 | 2.0 |
| C.B 31 C.F<br>ZZ 7463<br>27502 | 36 | | | 2.2 | 2.0 | 1.5 | 2.8 | 2.6 | 2.5 |
| N.V. 40 C.M.<br>XX 2103<br>37813 | 37 |  |  | 1.9 | 3.4 | 1.6 | 2.4 | 2.1 | 2.3 |
| G.F 23 C.F<br>AW 6203<br>17576 | 40 |  |  | 3.0 | 2.0 | 4.0 | 3.0 | 2.0 | 3.1 |
| C.S. 13 C M<br>B.D. 9681<br>76280 | 41 | | | 2.0 | 1.5 | 1.0 | 2.5 | 1.6 | 1.6 |
| L.S. 10 C.M.<br>BD 8740<br>75415 | 49 | | | 2.5 | 1.5 | 1.2 | 2.4 | 1.7 | 1.4 |
| F.S. 79 W.M<br>AF 7342<br>77781 | 50 | | | 3.0 | 2.5 | 2.7 | 2.5 | 1.8 | 1.6 |

Adrenals have been drawn to scale

After 72 hours, the radiographs were of no value for calculation In 4 cases, air did not fill one side, three cases had prior renal surgery and the fourth had had recurrent pyelonephritic episodes with questionable cortical abscesses as a child

*Measurement* For the purpose of initial measurement, the adrenal was considered an approximate triangle A line was drawn connecting the points of the base This measurement was designated the "base measurement " A second line was drawn from the apex of the adrenal shadow to the midpoint of the baseline The distance from the apex to the point where the line intersected the usually concave contour of the base of the adrenal shadow was designated "height measurement " In addition, the adrenal shadows were traced on graph paper and the surface area estimated (table 1)

*Right adrenal gland* The average "base measurement" was 2 5 cm (range 1 0 cm to 3 3 cm ), the average "height measurement" was 2 2 cm (range 1 4 cm to 4 0 cm ) and the average area was 2 0 cm (range 1 0 cm to 4 0 cm )

*Left adrenal gland* The average "base measurement" was 2 9 cm (range 2 4 cm to 5 0 cm ), the average "height measurement" was 2 0 cm (range 1 5 cm to 3 5 cm ), and the average area was 2 6 cm (range 1 4 cm to 8 2 cm )

## DISCUSSION

Although the patients selected for this study had nonendocrine diseases or recent trauma, it is conceivable that the size of their adrenal glands might have altered, however, these changes are probably insignificant

It has been suggested by many authors that carbon dioxide and oxygen are superior gases for this procedure because they are rapidly absorbed and, should gas embolism occur, the chances for recovery are greater Even though the use of room air may represent a hazard, we believe that its use is a calculated risk

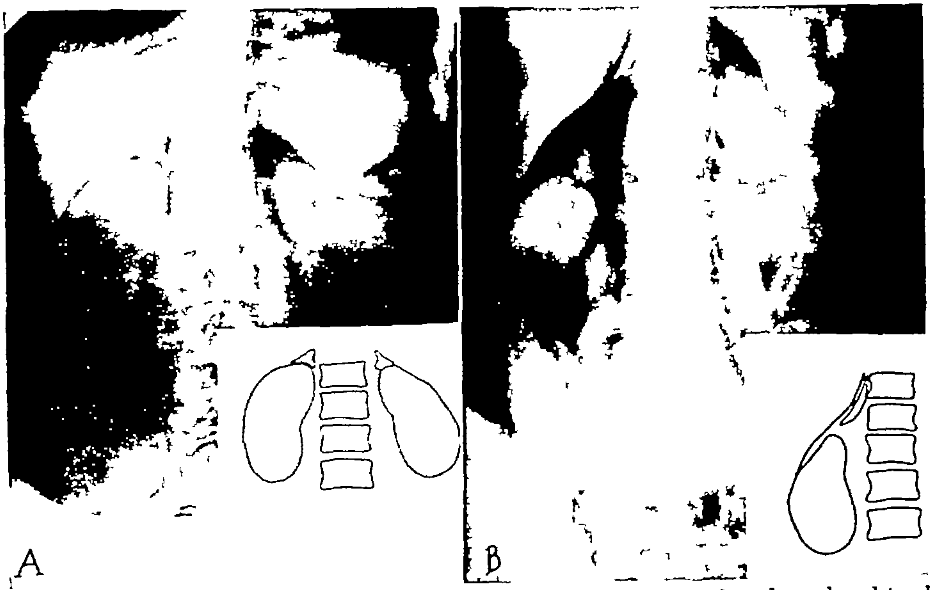


FIG 4 A typical normal adrenal roentgenograph *B*, normal wedge-shaped right adrenal variant

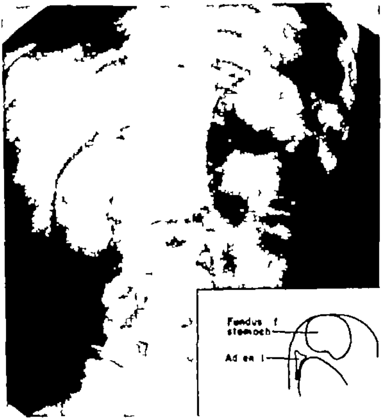


FIG 5 Collapsed fundus of stomach simulating adrenal mass

justified by the fact that the 24-hour films were of superior quality, permitting better visualization of the adrenal glands

Anteroposterior films were used for measurement as the magnification factor in this projection is less than in a postero anterior view

The right adrenal shadow more often conformed to the shape expected from descriptive anatomy textbooks (fig 4, A) In 2 cases, the right adrenal appeared as a thin wedged, elongated shadow, as described by Cahill (fig 4, *B*)

Only those cases in which the adrenal glands were completely outlined bilaterally, permitting accurate determination of both shape and measurement, were selected This eliminated the possibility of including unsuspected diseased adrenal glands in the series and explains why the percentage of visualization is low

In some instances it is difficult to define the margins of the adrenal gland in the pneumogram because of shadows cast by the connective tissue septa which appear to be more abundant in the adrenal area It is our impression that too much gas in the adrenal area may accentuate these extraneous shadows and impair visualization of the gland

It has been noted on several occasions by one of us (L C D ) that the fundus of the stomach will evacuate its gas when the subject is in the antero posterior position and cast a rounded shadow of soft tissue density immediately above the upper pole of the left kidney, simulating an adrenal mass (fig 5) This has been proved by laminography

Goodwin reports that the tail of the pancreas and the left lobe of the liver have been mistaken for adrenal masses

## SUMMARY

Presacral retroperitoneal air insufflation is a safe diagnostic procedure with a low morbidity and mortality For a gas, room air is preferred to oxygen or car bon dioxide Complications are minimal and of short duration Only two fatal cases of gas emboli are currently known resulting from this route of administration The treatment is briefly discussed

An average set of dimensions has been given to assist the diagnostician, enabling him to appreciate the variations in size of normal adrenal glands

Adequate roentgenological visualization of adrenal glands can be done in a sufficient percentage of cases to justify its being added to the diagnostic armamentarium of the physician

We believe that presacral retroperitoneal air insufflation gives prompt, valuable, visual information about the size, shape and position of adrenal glands, and that air studies should be as much a part of adrenal evaluation as hormonal studies Positive preoperative roentgenographic demonstration of suspected adrenal disease aids the surgeon

*R H H , 109 Porter Bldg , Bryan, Texas*

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# ECHINOCOCCUS RENAL CYST CURED BY PARTIAL NEPHRECTOMY

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Echinococcus disease of the kidney is rare in man It is particularly rare on the North American continent, as indicated by the paucity of cases reported from this area In the JOURNAL OF UROLOGY, for example, from its first issue in February 1917 through the most recent in October 1955, there are only four papers on the subject One of these deals with the disease in New Zealand [1] Of the three[2–4] patients reported from American clinics, all were foreign born and had lived in the United States only 1, 3 and 12 years respectively Baurys[4] in 1952 stated that only 35 cases had been reported in this country In the medical literature from areas in which echinococcus disease is, or was, relatively frequent, such as Iceland, Australia,[5] New Zealand,[1, 6, 7, 8] Argentina,[9] Brazil, Southern Europe,[10, 11] the Middle East, and North Africa the percentage of kidney involvement varied from 0 65 per cent to 7 5 per cent, the average about 2 5 per cent Including countries like India[12] where hydatid disease is rare, about 245 cases of renal echinococcus have been recorded, in all

Taenia echinococcus granulosus is a small tapeworm inhabiting the upper part of the small intestine of the dog family (wolf, fox, jackal, dog) The adult worm which consists of only four segments, is 2 5 to 5 0 mm long The ova discharged in the excreta of the dog are ingested by cattle, swine and especially sheep, and occasionally by man, usually in childhood After the outer covering is digested away by the gastric juice, the embryos are liberated and find their way to the liver by entering the portal circulation Thence some filter through to the lungs Fewer still enter the systemic circulation by way of a patent foramen ovale or by traversing the pulmonary vascular system to reach the brain, spleen, kidney, etc Where arrested, they develop into cysts which grow very slowly Within them daughter cysts are formed From the inner layer or brood membrane develop larvae identical with the head or scolex of the definitive parasite, bearing four suckers and hooklets in a double row circle

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The disease occurs in man when he lives in close association with sheep and their shepherd dogs under unhygienic conditions In Holland, Snapper[13] pointed out in 1917 that hydatid disease was endemic where sheep were slaughtered without adequate sanitary inspection and the dogs ate discarded offal infested with hydatid cysts Humans can then be infected by the eggs present in the dogs' excreta

The distribution of hydatid disease in man is about the same in most parts of the world liver, 70 per cent, lungs, 10 per cent, except in Australia where lung involvement in children is 25 per cent,[14] spleen, 2 5 per cent, kidney, 2 per cent, other abdominal organs, 5 per cent, muscle and cellular tissues, 5 per cent, brain, 5 per cent, bone, 0 5 per cent It now appears that infection occurs in childhood and that the average cyst is almost as old as the patient harboring it

It is obvious that to reach the kidney, the echinococcus embryo must pass through both the portal and pulmonary circulation, unless there is a patent septum or foramen ovale Lodged in the renal cortex the hydatid cyst gradually enlarges, compressing renal tissue, causing displacement of renal pelvis and calyces, obstructive phenomena with infection or calculus formation Calcification of the cyst wall may occur Perforation into the outflow system may result in renal colic due to passage of daughter cysts or calcific material Secondary infection supervening may result in pyelonephritis or local renal suppuration Perforation outside the kidney may cause retroperitoneal involvement, of the peritoneal cavity, or through the diaphragm into the lung and bronchial system

## DIFFERENTIAL DIAGNOSIS[5] [15]

Hydatid disease of the kidney must be differentiated from polycystic kidney, solitary and multiple cysts of the kidney, renal neoplasm, carbuncle of the kidney, retroperitoneal tumors and cysts, splenic lesions Study of the urinary tract by intravenous urography, retrograde pyeloureterogram (plus perirenal insufflation except when secondary infection is suspected) and aortography when additional information is desired, is of value in demonstrating the resulting anatomic and functional changes of the affected kidney Laboratory methods,[16] however, are essential in arriving at the etiological diagnosis Highly suggestive is pronounced eosinophilia More reliable is the complement fixation test of Ghedini and Weinberg reported as 85 per cent positive, and the intradermal test of Casoni reported as 92 per cent positive In both reactions hydatid cyst fluid is used as the antigen These reactions are said to be positive in all taenia infestations, not only in echinococcus disease In open lesions hooklets, scolices or bits of laminated membrane may be found in the sediment of the urine

Therapy for *unilateral* renal echinococcus disease has been nephrectomy[5, 9, 10, 11, 17–19] when the other kidney is normal and adequate functionally If the lesion is too large, or grossly infected secondarily, if both kidneys are involved or if a solitary kidney is the site of the lesion, the practice has been to marsupialize the cyst and treat the inner lining with 2 per cent formalin[5, 26] The exposed cyst has also been aspirated and injected with formalin solution This should never be done through the abdominal wall for fear of leakage and severe anaphylactic reaction Although Kretschmer[21] suggested in 1923 resection when possible, no case of partial nephrectomy for echinococcus cyst of the kidney has been reported

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We present herewith the case history of a patient in whom the preoperative diagnosis of echinococcus cyst of the left kidney was made and confirmed and in whom the diseased segment with cyst intact was resected successfully, conserving the major part of the organ

## CASE REPORT

M Y , Beth El Hospital No 21351, male, Hebrew, aged 43, married, was admitted January 17, 1955, discharged February 17, 1955 Born in Russia, he went to Israel at age 13 where he lived in the Arab quarter of Haifa He served in the Israeli Army during the wars against the Arabs, from 1942 to 1948 There was a dog in his home from 1943 until his wife and he left for the United States in February 1953 He was a builder He never tended nor slaughtered sheep

In August 1929 he was stabbed in the left paraumbilical region He had to be transfused for serious blood loss in a hospital at Haifa, but he was not operated upon In 1942 he sustained shrapnel wounds in his left lower leg posteriorly

Two weeks before admission there was sudden onset of nausea, vomiting, and temperature elevation to 104F He was confined to bed with shooting pains in the left abdomen, neck, back, arms and legs His local physician prescribed terramycin, but he took only eight capsules of 250 mg each

On admission the blood pressure was found to be 125/75, pulse rate 80 per minute, respirations 24 per minute, temperature 101 8F The latter rose to 102 8F but subsided to 98 8F on the third day remaining thereafter below 100F without specific drug therapy On physical examination the positive findings were enlarged tonsils, congested pharynx and fauces, small nodes in neck and axillae, systolic murmur at the apex In the left upper quadrant of the abdomen a tender mass was palpated extending into the flank Some observers thought it to be a large spleen but others considered it renal because its lower border was rounded and it was ballottable into the loin It moved with respiration There was some dullness at the left base but the lung moved freely with respiration

Voided urine was negative except for occasional erythrocytes, three to four

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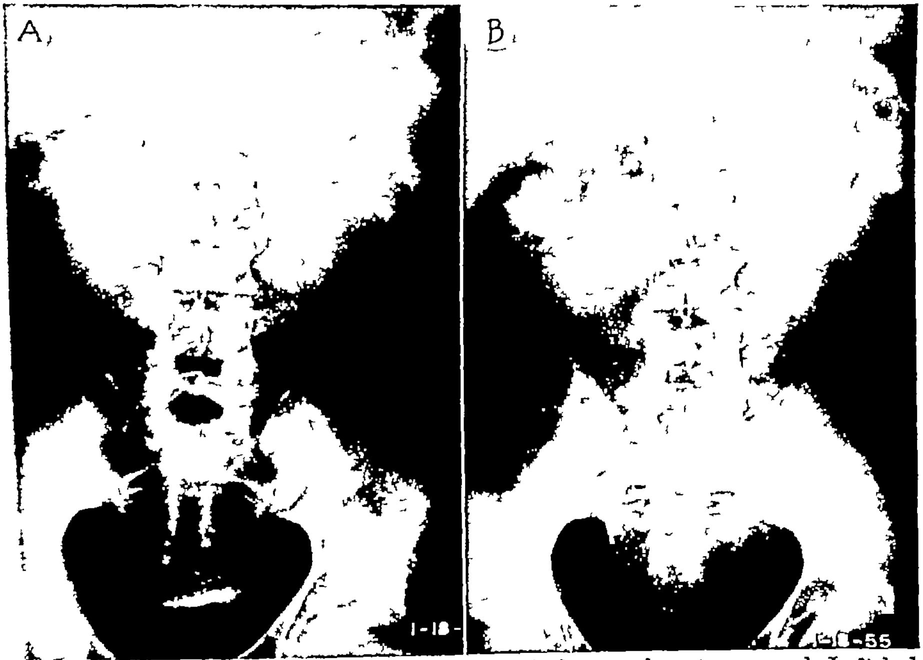
leukocytes and an occasional hyaline cast per high power field Urea clearances 79 per cent and 115 per cent Phenolsulphonphthalein excretion 42 per cent in 2 hours Stool negative for ova and parasites Sedimentation rate 7 mm per hour (Wintrobe), hematocrit 43, hemoglobin 14 gm White blood count 23,000, segmented 55, stabs 15, eosinophils 16, lymphocytes 14 Mazzini test negative Blood chemistry determinations glucose 97 mm per cent, urea nitrogen 15 mm per cent, total protein 7 1 gm per cent, albumin 3 9 gm per cent, globulin 3 2 gm per cent, calcium 9 8 mg per cent, phosphorus 2 3 mg per cent, alkaline phosphatase 4 King-Armstrong units, thymol turbidity 2 units, cephalin flocculation 4+ Cholesterol 164 mg per cent of which 38 per cent were nonesterified Blood culture was negative on three occasions

Roentgen examination of the chest showed the left diaphragm elevated with some fluid in the costophrenic sinus but on fluoroscopy the diaphragm moved freely Excretory urography on January 18 showed the right kidney calyces and pelvis and ureter normal[1] with well-defined psoas margin On the left side the psoas margin was obscured by a poorly outlined mass under the diaphragm occupying the splenic and renal areas There was good excretion, the renal pelvis was small, the calyces large and rounded, but these structures were displaced markedly cephalad and laterally and the kidney was apparently rotated The upper third of the ureter was not visualized, the lower third appeared about normal in position but contained a small calculus 3–4 mm in length at the level of the ischial spine (fig 1)



[illegible] excretory urogram, 5 minutes Right kidney and ureter normal Left kidney [illegible] completely filled, calcyes dilated and clubbed Left psoas margin obscured by mass [illegible] urogram, 60 minutes Right outflow tract emptied out Retention in left kid- [illegible] renal pelvis, dilated calyces Displacement and rotation Small calculus in [illegible]

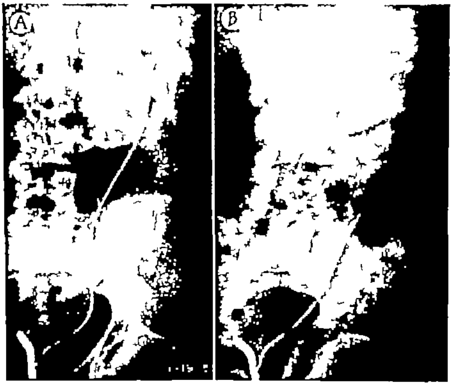


FIG 2 *A* left retrograde pyelogram Upper ureter displaced laterally and apparently leaves lateral aspect of renal pelvis Small calculus in contact with catheter *B* left retrograde pyelogram left oblique exposure Demonstrates renal rotation pelvis anterior, calyces posterior Upper ureter displaced far anteriorly coursing downward in front of a mass Small calculus in left lower ureter in contact with catheter

The following day cystoscopy and ureteral catheterization with left retrograde pyeloureterogram were accomplished (Dr Henry Bloomberg) In cultures of urine from the bladder and each kidney, hemolytic staphylococci, sensitive to chloromycetin and magnamycin, were found Indigo carmine, injected intravenously, appeared from the right side in 5 minutes in good concentration, from the left side in 20 minutes in poor concentration A catheter was placed in the left ureter and a left pyeloureterogram made The roentgen studies carried out in anteroposterior and left oblique positions showed the small calculus in the lower ureter in close contact with the catheter The ureter was dislocated to the left and far anteriorly by a retroperitoneal mass in front of which it coursed As on the excretory urography the renal pelvis and its dilated calyces were displaced upward, laterally, and rotated (fig 2)

The impression of the urologists was at first that the patient had expelled a small calculus from an anomalous "cake" kidney down into the left lower ureter with accompanying pyelonephritis This would have explained the pain, fever and leukocytosis but not the eosinophilia Under further observation the leukocytosis declined in 48 hours from 23 000 to 14 000 per cubic mm , but the percentage of eosinophils rose to 35, 40, then 50 This rise seemed to occur with each further examination of the patient by cystoscopy, pyelography, abdominal palpation The erythrocyte sedimentation rate rose to 28 mm per hour (Wintrobe) The first impression was therefore abandoned and it was concluded that echinococcus cystic disease involving the lower pole of the left kidney could well explain the eosinophilia, the clinical course and the roentgen studies Serum for echinococcus complement fixation sent to the New York City Bureau of Health laboratories was reported 4+, (the day after surgery had been performed) It is of interest that the reaction was still present in the serum when the patient was ready for discharge from the hospital The reaction has been known to persist for a year when the disease has been successfully eradicated Persistence beyond that period is said to indicate another focus in the patient

By the time retroperitoneal exploration had been agreed upon by the medical department and the urological division, the patient was afebrile, up and about, and the ballottable renal mass was no longer tender The opinion of some observers however was inclined to the diagnosis of retroperitoneal Hodgkin's disease

Operation was performed (P W A ) January 27, 1955 under spinal nupercaine analgesia using Jones' solution Incision left oblique over twelfth rib from border of the rectus abdominis to angle of rib, then upward over eleventh and tenth ribs paraspinally The twelfth rib was resected together with segments of 3 cm of the eleventh and tenth ribs without pleural injury (Nagamatsu's incision) The fascia of Gerota was incised over the entire length of the underlying renal mass Findings Left suprarenal gland normal Upper third of the mass was normal kidney tissue rotated so that the convex border lay posteriorly, the renal pelvis and ureter anteriorly The latter passed downward and forward densely adherent to the peritoneum anteriorly and to an elastic mass 15 cm in diameter posteriorly The mass was within the stretched-out renal capsule, and the inflamed perirenal fat bound it to the peritoneum anteriorly and to the parietes posteriorly The renal

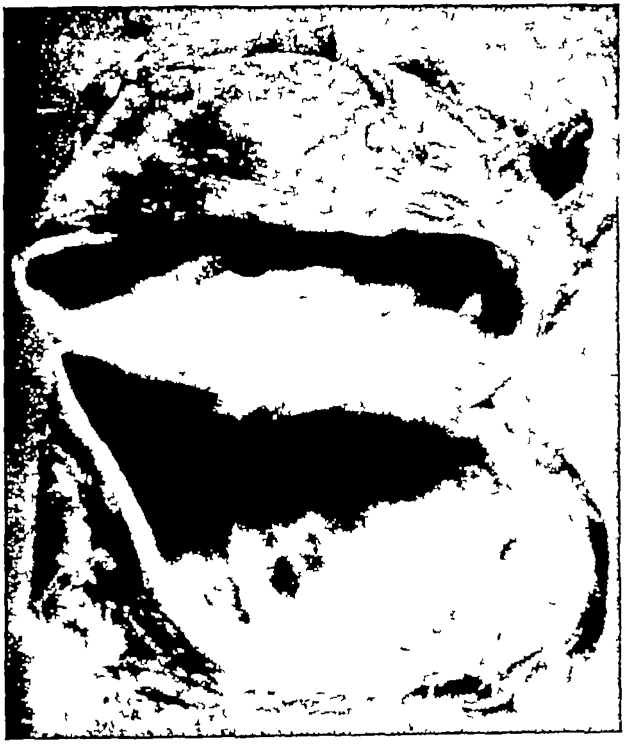


FIG 3 Mass resected from left kidney, lower pole Specimen transected Shows wall of cyst and surrounding rim of kidney tissue which invested it Uncovered area of cyst was in contact with lower margin of renal pelvis and elongated lower calyx

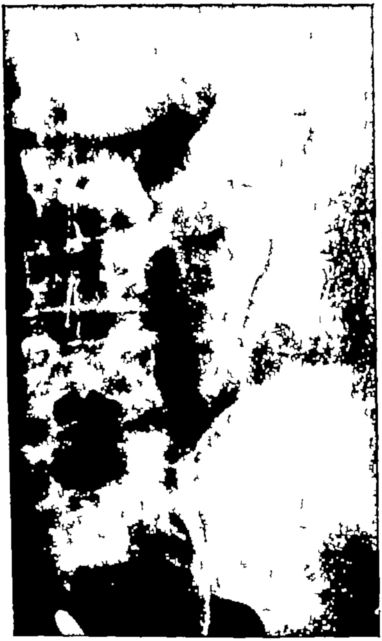


Fig 4 Left retrograde pyeloureterogram 3 months after operation Renal pelvi normal position, moderately enlarged calyces less dilated, less blunted Upper ure angulated due to adhesion to line of renal repair

vascular pedicle entered anteriorly just above the renal pelvis and contained eral enlarged lymph nodes, one of which was removed for examination Proced By blunt and sharp dissection the entire kidney with its lower pole mass was t and delivered The ureter was dissected from the peritoneum which was a dentally opened and repaired The ureter was traced upward to the renal pelvis Kidney tissue was found thinned out anteriorly and posteriorly over the large cystic mass An incision was made through the renal capsule and renal tissue in a transverse direction This led to a thick-walled cyst which could now be separated from the lower margin of the renal pelvis and its elongated lower calyx The mass having been removed intact, kidney capsule and underlying renal tissue were approximated with interrupted chromic catgut sutures so as to cover the exposed pelvis and calyx Only one blood vessel required ligation The conserved upper two thirds of the kidney were reposited in normal position under the diaphragm A rubber dam was placed around the lower reconstructed margin and a packing was placed to hold the organ up in place Closure Muscles and fascia were approximated with figure 8 sutures of chromic catgut The drains were brought out at the angle of the wound The skin was closed with silk sutures

Pathological report (Dr David H Spain) The lymph node showed nonspecific inflammatory changes The mass proved to be a cyst with walls 1 cm in thickness, lined by whitish membranous material It was filled with a pinkish-tinged fluid containing hooklets and cholesterol crystals No daughter cysts were noted (fig 3) Diagnosis Echinococcus cyst

Postoperative course Although no unusual blood loss occurred during the procedure, the patient's hemoglobin declined from 11 2 to 9 5 gm The leukocytes diminished from 14,000 to 9,800 per cubic mm Eosinophils diminished from 50 to 8 per cent Hematocrit declined from 42 to 33 The erythrocyte sedimentation rate remained at 28 mm per hour (Wintrobe) Temperature remained below 101F until the drains were removed on February 2, the sixth postoperative day It then rose to 102F after a mild chill On February 7, the eleventh day after operation, about 100 cc of pus was evacuated from the depth of the wound at the drainage site and a latex tube inserted Culture of the pus yielded hemolytic Staphylococcus as had been found in the urine before surgery The organism was coagulase positive and sensitive to erythromycin, chloromycetin and terramycin

Despite the administration of appropriate antibiotics, the wound continued to drain moderately until May 10 On May 15, a checkup cystoscopy and left retrograde pyeloureterogram revealed that renal pelvis and calyces were moderately dilated, because the upper ureter was angulated and adherent at the repaired renal tissue suture line (fig 4) The small calculus noted before operation was no longer demonstrable The patient had not observed its passage The urine was clear, pH 5 0, microscopic examination negative The patient had no subjective complaints, felt well enough to have resumed work, and had gained weight

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# LONGEVITY FOLLOWING NEPHRECTOMY

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The thought of having a kidney removed causes great unhappiness to a patient. A mental hazard is immediately added to the disturbed physical condition which already exists. Many thoughts of the unknown future penetrate the mind so that the urologist is confronted with several questions which he must be prepared to answer: 1) Can I live a normal life with one kidney? 2) Will longevity be interfered with? 3) Will I be compelled to live a restricted life, as far as work activities, diet, indulgence in athletic sports, marriage, and pregnancy are concerned? 4) Will I have difficulty in obtaining insurance?

In order that those questions might be answered satisfactorily and intelligently, it was decided to analyze all cases of nephrectomy on the urologic service at the Sinai Hospital from 1918 to 1954 inclusive, a period of 36 years. These patients were operated upon by six qualified urologists and the various residents in urology. Approximately 79 per cent of these operations were performed by two surgeons (Dr. A. E. Goldstein and Dr. B. S. Abeshouse).

Questionnaires, personal letters to the patient or families, telephone communications and personal examinations, where possible, were made in this group of 591 cases (table 1).

The classification of the lesion for which these nephrectomies were performed included a larger variety than those reported by others (tables 2 and 3).

Unfortunately, the few studies previously made have not been over a sufficient period of years so that we are unable to make many comparisons. This is undoubtedly due to the fact that not many nephrectomies were performed before the beginning of this century.

Deming in 1938 stated that, "the first successful nephrectomy was performed by Dr. Erastus Bradley Wolcott of New York in 1861 and was followed by Dr. Gustave Simon of Heidelberg in 1869. After that, few nephrectomies were performed successfully for many years. The failure of Paul Von Brun in 1870 caused a discontinuance of the procedure until after aseptic surgery."

The contributions by the Russian physician Solovov in 1933 and Deming, Kretschmer and Mathé in this country were probably the most important ones made up to 1945.

It is interesting to note that our largest group of nephrectomies was performed for renal neoplasm (107), the second, for calculous pyonephrosis (106). These two groups, plus the group of hydronephrotic cases, make up more than fifty per cent for which nephrectomy was performed.

In any group of cases in which nephrectomy is accomplished, one always finds it necessary to perform secondary operations.

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Read at annual meeting, American Urological Association, Los Angeles, Calif., May 16–19, 1955.

TABLE 1

| | |
|---|---|
| Questionnaires sent to patients or families | 591 |
| Questionnaires answered, letters received/or examinations made | 391 (66 1%) |
| Unknown whereabouts or condition of patient up to 1955 | 200 (33 0%) |
| Statistics from answers and examinations | 391 cases |
| Living to date | 253 (64 7%) |
| Dead to date | 138 (35 3%) |

TABLE 2 *Classification of pathological process for which nephrectomy was performed*

| | | | | | |
|---|---|---|---|---|---|
| 1 | Renal neoplasm | 107 | 11 | Renal atrophy | 6 |
| 2 | Calculous pyonephrosis | 106 | 12 | Renal trauma | 3 |
| 3 | Hydronephrosis | 91 | 13 | Renal polycystic degen | 4 |
| 4 | Renal calculi | 71 | 14 | Calculous hydronephrosis | 4 |
| 5 | Pyonephrosis | 54 | 15 | Aneurysm of renal artery | 2 |
| 6 | Pylonephritis | 44 | 16 | Renal infarction | 2 |
| 7 | Renal tuberculosis | 38 | 17 | Hemangioma | 1 |
| 8 | Renal cong malformation | 15 | 18 | Nephrosclerosis | 1 |
| 9 | Renal cysts | 10 | 19 | Urinary fistula | 1 |
| 10 | Renal ptosis | 9 | 20 | Papillitis | 1 |
| | Lost case histories | | | | 21 |
| | Total nephrectomies | | | | 591 |

TABLE 3 *Longevity after nephrectomy*
Other Authors

| Author | Year | Cases | Study P O Years | Per Cent P O Mortality |
|---|---|---|---|---|
| Fisher | 1927 | 100 | 5 | 7 0 |
| Prather and Crabtree | 1933 | 296 | no data | 1 01 |
| Solovov | 1933 | 205 | no data | no data |
| Posner | 1935 | 241 | no data | no data |
| Deming | 1938 | 180 | 15 | 3 9 |
| Kretschmer | 1943 | 156 | 25 | no data |
| Mathé | 1945 | 247 | 25 to 30 | 2 to 3 |
| Rioseco and Baezo | 1948 | 90 | 6 5 | 1 1 |
| Freeman | 1949 | 3 | 27, 35, 43 | None—only 3 cases |
| Coppridge, Roberts and Hughes | 1952 | 270 | no data | 1 0 |
| Rodriguez, Toland and Schwartz | 1954 | 227 | 10 | 004 |
| Goldstein | 1955 | 591 | 36 | 2 2 |

Since the kidney is a vital organ of the body, an important role of the urologist is to preserve as much renal tissue as is possible Therefore, considerable thought must be given before a kidney is sacrificed In cases of calculous hydronephrosis or pyonephrosis, the decision to remove either the stone or perform a nephrectomy is an important one with which urologists are daily confronted Many kidneys which formerly would have been sacrificed are now preserved because of advances in chemotherapy, conservative procedures and improved techniques

It is with this idea of conservatism that occasionally more than one surgical procedure is performed on the kidney, short of nephrectomy, but frequently ends by necessity in a secondary nephrectomy We have performed 64 (10 8 per cent) secondary nephrectomies (table 4)

Whereas secondary nephrectomy is a more hazardous procedure in our series there were no immediate or early deaths, and the procedure has not contributed, as far as we can determine, to a shorter span of life

The youngest patient upon whom we performed nephrectomy was 9 months of age The diagnosis was Wilms' tumor Operation was accomplished December 28, 1951 The child is alive and well

The oldest patient was a man of 82 who underwent nephrectomy for pyelonephritis on April 8 1947 The questionnaire that was sent him has not been returned

Seventeen (2 8 per cent) of our patients were children under 10 years of age, an additional 21 (3 6 per cent) were under 20 years The largest group of patients, 553 (93 6 per cent) were operated upon between the second and seventh decades of life (table 5)

The pathological process that necessitated nephrectomy did not particularly

TABLE 4 *Secondary nephrectomy*

| | Cases |
|---|---|
| Renal calculi | 21 |
| Hydronephrosis | 13 |
| Pyelonephritis | 10 |
| Calculous pyonephrosis | 6 |
| Pyonephrosis | 4 |
| Renal trauma | 3 |
| Renal congenital malformation | 2 |
| Tuberculosis | 1 |
| Renal neoplasm | 1 |
| Renal infarction | 1 |
| Hemorrhage | 1 |
| Renal ptosis | 1 |
| Total | 64 |

TABLE 5 *Age of patients*

| | |
|---|---|
| 1 mo to 1 yr | 2 |
| 1 yr to 2 yrs | 2 |
| 3 yrs to 5 yrs | 5 |
| 6 yrs to 10 yrs | 8 |
| 11 yrs to 20 yrs | 21 |
| 21 yrs to 30 yrs | 60 |
| 31 yrs to 40 yrs | 116 |
| 41 yrs to 50 yrs | 131 |
| 51 yrs to 60 yrs | 127 |
| 61 yrs to 70 yrs | 83 |
| 71 yrs and older | 15 |
| Lost case histories | 21 |
| Total | 591 |

TABLE 6 *Side and sex of patients*

| Right | Left | Male | Female |
|---|---|---|---|
| 182 | 161 | 194 | 149 |
| 59 | 66 | 82 | 43 |
| 6 | 7 | 6 | 7 |
| 4 | 4 | 7 | 1 |
| 6 | 6 | 7 | 5 |
| 6 | 4 | 7 | 3 |
| 33 | 26 | 44 | 15 |
| 296 | 274 | 347 | 223 |
| Lost case histories | | | 21 |

TABLE 7 *Post-nephrectomy and pregnancy*

| | |
|---|---|
| Single females (at time of operation) who later married and became pregnant | 5 |
| Married females who later became pregnant | 6 |
| Difficult pregnancies | 0 |

bear any relationship to sex, although more male patients (347) required operation than females (223) The involvement of one kidney or the other did not seem to bear any relationship in any way In our series, nephrectomy was performed 296 times on the right side, 274 times on the left (table 6)

Study of the group of post-nephrectomy and pregnancy cases yielded interesting results, even though our series was small (table 7) The question arises frequently as to advisability of pregnancy after nephrectomy

These patients were watched and studied carefully In no case did the opposite kidney cause any disturbance There were no elevations of blood pressure, nor pain in the opposite kidney, nor any albumin or casts found in the urine In one post-nephrectomy case, interruption of pregnancy and ligation of the fallopian tubes were advised because of the condition of the opposite kidney

Prather and Crabtree studied thoroughly the pregnant woman and concluded that nephrectomy was not a contraindication to pregnancy In their group of 296 cases of nephrectomy, 55 per cent were tuberculosis of the kidney In accumulated statistics that they have collected, the mortality rate was between 1 09 to 1 4 per cent

Undoubtedly, instances exist where in the presence of a single kidney in a pregnant woman, interruption of pregnancy should be considered, particularly if the single kidney becomes damaged early in pregnancy and if renal complications become evident late in pregnancy One such case occurred in our series

Posner, who also studied the condition carefully, concluded that pregnancy following nephrectomy pursues a rather normal course and attempted to prove that, if the remaining kidney is normal, no disturbance should be encountered In cases of nephrectomy for tuberculosis, he recommended waiting several years before pregnancy was considered Kanter and Klawans advocated sterilization in all cases where nephrectomy was performed for tuberculosis

The question of early or immediate mortality depends a great deal on the condition of the patient rather than upon the age, assuming that all things are equal, such as the experience and judgment of the surgeon, careful diagnosis the preliminary care that the patient has received, as well as the immediate postoperative care Complicated conditions present at the time of operation and careful handling of tissues are extremely important and demand careful attention We have always prepared our patient preoperatively as well as possible and have always given at least one pint of blood during the operative procedure Chemotherapy was instituted postoperatively in all cases Early ambulation was encouraged wherever possible

Because of all the precautions taken, we have been fortunate to have a minimum of early deaths, 13 (2 2 per cent), several of which were not due to the operative procedure Nevertheless, we have classed them as early postoperative deaths (table 8)

A review of our early postoperative deaths discloses that in six (46 per cent) the cause was shock from 45 minutes to 96 hours following operation All 6 patients were poor operative risks due to complications One patient died on the table from hemorrhage In that case an aberrant renal vessel was cut across One patient had a severe myocardial condition prior to operation and another had an unrecognized coronary disease One patient died of adrenal insufficiency The adrenal was accidently removed. Autopsy was not permitted

Most of these deaths occurred early, possibly with present advances in chemotherapy and technique, some might not have occurred

Nephrectomy was performed for tuberculosis in 38 (6 4 per cent) cases All the patients were carefully studied and a positive diagnosis made In the early cases no prescribed method of treatment existed aside from surgery

In our series, no case occurred before the age of 13 years There were 3 cases between 13 and 20 years, 25 cases (66 per cent) were in the second and third decades of life, one occurred during the sixth decade Of the 38 patients 26 (68 per cent) were followed and examined (tables 9 and 10)

Interesting enough, the patient who lived the longest in our series of 391

TABLE 8 *Post nephrectomy early mortality*

| | Name | Age | Diagnosis | P O Death | Cause of Death |
|---|---|---|---|---|---|
| 1 | A N | 61 | Pyonephrosis | 45 mins | Shock |
| 2 | L S | 62 | Pyelonephritis | 1 hour | Hemorrhage |
| 3 | W H | 47 | Renal calculus | 16 hours | Shock |
| 4 | S B | 50 | Cal cystic kidney | 24 hours | Shock |
| 5 | S R | 62 | Neoplasm | 24 hours | Shock |
| 6 | B H | 55 | Pyelonephritis | 44 hours | Adrenal insufficiency |
| 7 | A K | 62 | Neoplasm | 2 days | Shock |
| 8 | M W | 64 | Cal pyonephrosis | 2 days | Myocardial disease |
| 9 | A B | 55 | Hydropyonephrosis | 2 days | Septicemia |
| 10 | C G | 70 | Cal pyonephrosis | 3 days | Cardiac |
| 11 | G R | 58 | Pyelonephritis horseshoe kidney | 3 days | Coronary disease |
| 12 | J T | 36 | Tuberculous pyoneph | 3 days | Venous thrombosis |
| 13 | D W | 41 | Acute pyelonephritis | 4 days | Shock |

13 (2.2 per cent) postoperative mortality

TABLE 9 *Nephrectomy for renal tuberculosis*
Ages of patients

| Ages | No Cases |
|---|---|
| 13 yrs to 20 yrs | 3 |
| 21 yrs to 30 yrs | 11 |
| 31 yrs to 40 yrs | 14 |
| 41 yrs to 50 yrs | 6 |
| 51 yrs to 60 yrs | 3 |
| 61 yrs and above | 1 |
| Total | 38 |

TABLE 10 *Nephrectomy for renal tuberculosis*

| | Living | Dead |
|---|---|---|
| 1 day to 3 days | 0 | 1 |
| 5 days to 6 mos | 0 | 1 |
| 6 mos to 1 yr | 1 | 0 |
| 2 yrs to 5 yrs | 5 | 3 |
| 6 yrs to 10 yrs | 5 | 2 |
| 11 yrs to 15 yrs | 0 | 0 |
| 16 yrs to 20 yrs | 3 | 0 |
| 21 yrs to 25 yrs | 1 | 0 |
| 26 yrs to 30 yrs | 1 | 0 |
| 31 yrs to 36 yrs | 3 | 0 |
| Total | 19 (73 per cent) | 7 (27 per cent) |

TABLE 11 *Nephrectomy for renal tuberculosis*
Other Authors

| | No | Series | Per Cent |
|---|---|---|---|
| Coppridge, Roberts and Hughes | 14 | 270 | 5 |
| Rioseco and Baezo | 63 | 90 | 70 |
| Kretschmer | 49 | 156 | 31 4 |
| Deming | 36 | 120 | 30 |
| Fisher | 24 | 100 | 24 |
| Prather and Crabtree | 163 | 296 | 56 |
| Goldstein | 38 | 591 | 6 4 |

traced cases is one who was operated upon for renal tuberculosis in 1918 at the age of 27 and is still alive and well 36 years postoperatively at the age of 63 years

In the 26 traced nephrectomy cases for renal tuberculosis, 19 (73 per cent) are living and 7 (27 per cent) are dead The length of life of the living cases up to 1955 is from 1 to 36 years or an average of 13 years

The span of life of patients who died up to 1955 was from 3 days to 10 years with an average of 2 7 years

The youngest patient operated upon for renal tuberculosis was aged 13 years in 1928 He is still alive in 1955 at the age of 40 years

The oldest patient operated upon for renal tuberculosis was aged 67 He is *still alive in 1955 at the age of 74.*

The existence of renal tuberculosis seems to depend on geographical location, since the percentages vary greatly in the reported cases of other authors (table 11)

Our largest series of cases with the shortest span of life after nephrectomy is *that group comprised of various types of renal neoplasms (table 12)* This group consists of 107 patients (18 1 per cent) Of the 107, we were able to trace the patients or records of 83 (77 5 per cent) See table 13 In the total group of 107 cases, 6 were between the ages of 1 month and 5 years, while 95 (90 per cent) were between the ages of 31 and 70 years Five patients were operated upon for renal neoplasm more than 70 years of age

Five of our traced patients died within 6 months of the operation, while 39 of 49 patients died within 5 years compared to 24 who lived as long as 5 years Five patients lived as long as 10 years and 5 as long as 15 years

Studies by other authors who have performed nephrectomies for neoplasm have not shown quite so high a percentage of tumors in their group as ours

Most authors have demonstrated the occurrence of renal neoplasm from 7 1

TABLE 12 *Nephrectomy for neoplasm*
Ages of patients

| Ages | No |
|---|---|
| 1 mo to 5 yrs | 6 |
| 21 yrs to 30 yrs | 1 |
| 31 yrs to 40 yrs | 8 |
| 41 yrs to 50 yrs | 10 |
| 51 yrs to 60 yrs | 46 |
| 61 yrs to 70 yrs | 22 |
| 70 yrs and above | 5 |
| Total | 107 |

TABLE 13 *Nephrectomy for neoplasm*

| | 1955 | |
|---|---|---|
| | *Living* | *Dead* |
| 1 day to 3 dys | 0 | 2 |
| 3 dys to 6 mos | 0 | 3 |
| 6 mos to 1 yr | 9 | 22 |
| 2 yrs to 5 yrs | 15 | 12 |
| *6 yrs to 10 yrs* | 5 | 5 |
| 11 yrs to 15 yrs | 5 | 4 |
| 16 yrs to 20 yrs | 0 | 0 |
| 21 yrs to 30 yrs | 0 | 1 |
| 31 yrs to 36 yrs | 0 | 0 |
| Total | 34 (41 per cent) | 49 (59 per cent) |

to 12 per cent except Deming whose percentage was 19 4 per cent against ours of 18 1 per cent (table 14)

In the 83 traced nephrectomy cases for neoplasm, 34 (41 per cent) are living and 49 (59 per cent) are dead up to 1955

The span of life of those patients living to 1955 is from 1 to 15 years or an average of 4 7 years

The span of life of patients who died up to 1955 was from 1 day to 21 years with an average of 4 1 years

The youngest patient operated upon for renal neoplasm was 9 months old in 1951 He is still alive at the age of 5 to 1955

The oldest patient operated upon for renal neoplasm was 79 in 1950 He died in 1953

Of the total group of 391 traced nephrectomy cases, 253 (64 7 per cent) were living up to 1955 while 138 (35 3 per cent) were dead up to 1955 (table 15)

These figures include the deaths among cases for neoplasm and tuberculosis, both of which groups had a shorter span of life Death occurred sooner than in other groups

The span of life following nephrectomy in the groups other than tuberculosis and neoplasm is good and in most instances life was not affected or shortened in any way It appears that the supplementary action of the remaining kidney is almost always sufficient for vital necessities

Following nephrectomy, in 6 cases, the opposite kidney was operated upon for a pathological condition which existed prior to nephrectomy

TABLE 14 *Nephrectomy for renal neoplasm*
Other Authors

| | No | Series | Per Cent |
|---|---|---|---|
| Coppridge, Roberts and Hughes | 29 | 270 | 10 7 |
| Rioesco and Baezo | 7 | 90 | 7 8 |
| Kretschmer | 11 | 156 | 7 1 |
| Deming | 35 | 180 | 19 4 |
| Fisher | 12 | 100 | 12 0 |
| Goldstein | 107 | 591 | 18 1 |

TABLE 15 *Patients subjected to nephrectomy, living or dead to 1955*

| | Living | Dead |
|---|---|---|
| 1 day to 4 dys | 0 | 13 |
| 5 dys to 6 mos | 0 | 22 |
| 6 mos to 1 yr | 32 | 30 |
| 2 yrs to 5 yrs | 72 | 35 |
| 6 yrs to 10 yrs | 68 | 18 |
| 11 yrs to 15 yrs | 34 | 10 |
| 16 yrs to 20 yrs | 21 | 5 |
| 21 yrs to 30 yrs | 20 | 5 |
| 31 yrs to 36 yrs | 6 | 0 |
| Total | 253 (64 7 per cent) | 138 (35 3 per cent) |

In 3 cases a pathological process developed in the opposite kidney after nephrectomy In these 3 cases the blood chemistry became elevated and was reduced after the operation on the single kidney

Patients who had hypertension prior to nephrectomy showed no improvement except in 3 cases in which the operation was performed for congenital renal atrophy Following nephrectomy in these 3 cases, the blood pressure was reduced only to become elevated again from 3 to 15 years The blood pressure did not rise in any case following nephrectomy

In the cases of infection, the pyuria subsided in all instances after nephrectomy except in those where infection existed in the other kidney prior to operation

In those cases of nephrectomy for trauma (three) the patients were operated upon at the ages of 26, 11, and 8, and are still alive and in good condition 2, 19 and 21 years respectively The opposite kidney in each case is still normal Schatz believes that the removal of one kidney following an accident or otherwise does not impair the physical strength, provided no complications set in and that the opposite kidney remains in good condition Rotolo, in a study of work efficiency following nephrectomy, claimed that these patients enjoy normal health except that they are less resistant to infections

The pyelographic pictures were not altered in the remaining kidney after nephrectomy except in those cases where it was defective before operation

## SUMMARY

Nephrectomy was performed on 591 patients for various types of pathological conditions Through various means of followup, it was possible to study in some detail the outcome of 391 cases Nephrectomy for neoplasm comprised our largest group while nephrectomy for tuberculosis occurred about one-third as often

The average life span after operation for renal tuberculosis in the cases living to 1955 was slightly better than 13 years, whereas in those who died before 1955, it had only been 2 7 years Eight of 19 patients were living after nephrectomy for tuberculosis between 15 and 36 years One isolated case of nephrectomy for renal tuberculosis had a life span of 36 years

The average life span in nephrectomy for neoplasm among those patients who were living to 1955 was 4 7 years while among those who died prior to 1955, the survival had been approximately 4 1 years In isolated cases of nephrectomy for renal neoplasm the patients lived as long as 15 and 21 years

On the whole the outlook has been gloomy in both groups but considerably better in tuberculosis

In the cases of nephrectomy for renal calculi, infections, trauma and in pregnancies, survival is considerably better No change has been noticed in the life of the patient if the opposite kidney has remained normal

This improvement is due to better surgical technique improved chemotherapy, better and earlier diagnosis, blood transfusion, and improved technique in anesthesia

At no time need one hesitate to recommend nephrectomy provided the opposite kidney is in good condition What is needed is earlier diagnosis in all types of cases With the aid of newer drugs, we hope to avoid nephrectomy in some cases Preservation of renal tissue is very important, yet frequently nephrectomy can be considered a conservative operation

Experience and judgment will play a tremendous part in the conservation of renal tissue with an idea of increasing the survival rate

Patients can be assured and reassured that they need not have any fear in regard to undergoing nephrectomy when the decision is finally made Furthermore, our experience indicates that they can live as well with one kidney as with two, provided the opposite organ is in good condition at the start and remains so

We believe that a patient can live a normal life and that longevity need not be shortened except for those in whom nephrectomy is accomplished because of tuberculosis and neoplasm

We have not restricted our patients to any diet, work habits, exercise, marriage or pregnancy with the exception of those who had tuberculosis or neoplasm, and we have not found any difference in the end results

Relative to insurance, again we believe that from our studies these patients are no greater risks except those who have tuberculosis or tumor In spite of this observation, nephrectomy patients are given a high rate because insurance companies confuse these surgical cases with the various types of nephritides, certainly poorer risks The presence of albumin and casts in the urine after nephrectomy has occurred in only 2 cases except for those in which it existed prior to operation On the contrary, in some patients whose urine contained albumin and casts prior to nephrectomy, these elements disappeared after nephrectomy No patients demonstrated any marked increase in blood pressure except those in whom an associated condition developed In patients whose pressure was greatly elevated after nephrectomy, it invariably had been elevated beforehand

Our study demonstrates that there has been no interference with longevity in this group of patients after nephrectomy and living to 1955, excluding renal neoplasm and tuberculosis These patients demonstrate the presence of a healthy person, having lived postoperatively to 36 years, an average of 10 1 years Many are still alive, with a possibility of many more years of life Since 122 of the traced patients (exclusive of those operated upon for renal neoplasm and tuberculosis) were subjected to nephrectomy after 50 years of age, 81 or 66 per cent have already lived their average span of life of 65, and many more have gone beyond the average span of life The balance of those still alive have gone more than 10 years and still have the possibility of reaching, or going beyond, the average span This is a positive demonstration that patients undergoing nephrectomy can reach the average span of life of 65 years provided the opposite kidney is in good condition at the time of operation

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# EXFOLIATIVE CYTOLOGY AS AN AID IN THE DIAGNOSIS OF EARLY RENAL CARCINOMA

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Early diagnosis of cancer is of paramount importance if surgical removal of the lesion is to offer a favorable prognosis The notoriously insidious growth of malignancy and, in many instances, the late appearance of the cardinal symptoms may destroy the victim before surgery is effectively performed A test that will facilitate early diagnosis of malignancy deserves our earnest and serious consideration The histological investigation of desquamated cells, whenever available, is such a test and if expertly performed, should prove of invaluable service to the surgeon as well as patient

Exfoliative cytology, as a diagnostic laboratory procedure in neoplasms of the urinary tract, attracted wide attention in the last decade Review of the recent literature amazes one with the scarcity of controversial opinion Papanicolaou and Marshall[1], in 1945, first applied the smear test in the diagnosis of tumors in the urinary system Two years later the former[2] made the following statement "The application of the smear test in urological cancer diagnosis can be commended as a sound and dependable procedure which complements other means of diagnosis and helps in recognizing early or hidden malignant lesions " Chute and Williams[3] recommend the procedure in spite of the fact that, in their initial experience, a large percentage (45 per cent) of their reports were false negative Foot and Papanicolaou[4], and Schmidlap and Marshall[5] emphasize the special applicability of this method in early papillary carcinoma of the renal pelvis which is radiologically not demonstrable and which lesion can, justifiably, be regarded as "carcinoma in situ " Similar expression of opinion is voiced by Bunge and Kraushaar, Harrison and others[6, 7]

Ulfelder[8] summarizes his extensive experience with this problem as follows "Detection of cancer, while it is small and still unsuspected, should be the first duty of the cytologist It is a superior method for detecting asymptomatic cancer

A detailed discussion of the technique involved in this procedure is beyond the scope of this paper However, one may briefly state that the basic principle,

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Read at annual meeting South Central Section of American Urological Association San Antonio Texas, October 17-19, 1955

[1] Papanicolaou G N and Marshall, V F Cytology as applied to the urinary tract Science 101. 519 1945

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[7] Harrison, J H et al Smear of the urinary sediment in the diagnosis of neoplasm of kidney and bladder Surg., Gynec & Obst 92 129, 1951

[8] Ulfelder H Exfoliative cytology New Eng J Med 250· 911 1954

upon which positive reports are issued, depends upon the experience of the pathologist to differentiate the tumor cell from the numerous normal cells encountered on the smear Fundamental criteria of identification of the tumor cell have been adopted by various investigators in the field and these are succinctly stated by Chute and Williams[3] a) marked variation in the size and shape of the cell, b) dark hyperchromatic staining nuclei, c) the presence of giant nuclei, d) relative increase of the nuclei in their ratio to the amount of cytoplasm

Admittedly cytologic reports, by their nature so heavily dependent upon the personal equation, are subject to error and one must constantly guard against the possible pitfalls of the erroneous identification of the malignant cell While the false-negative reports detract from the dependability of the test, the false-positive may, and often do, lead to tragic consequences The experience and the keen eye of the pathologist will reduce the possibility of such errors to a minimum

The most vociferous opponent of this diagnostic procedure is J R McDonald of the Mayo Clinic Addressing a group of pathologists, McDonald[9] renounced the test as unreliable because of a large percentage of false-negative reports and a lesser, yet ominous, number of false-positive "Out of 78 cases of suspected lesions in the bladder only 36 showed tumor cells in the urine Of 84 cases of renal neoplasms tumor cells were identified in only 19 of which six were false-positive " While these figures are so obviously impressive in the support of his critically negative attitude one may find that, on closer analysis, they are not as foreboding as they appear McDonald omits a detailed classification of the types of neoplasm embraced by his figures

It is generally admitted that parenchymatous renal lesions and the invasive squamous cell type of carcinoma, involving the renal pelvis, ureter, and/or bladder, do not exfoliate typical cancer cells in sufficient number to be of reliable diagnostic value in the examination of the urinary sediment by the Papanicolaou method In cases of papillary neoplasms, however, desquamation occurs early and is sufficiently prolific to render the smear of the urinary sediment a dependable test in early lesions not yet demonstrable by any other method This I say with all due deference to McDonald's deserving eminence as a pathologist

The problem that I present falls in the category of cases in which a conclusive diagnosis could not be made with the orthodox diagnostic procedures at our disposal

J L , a 59-year-old man, fell 14 feet from the roof of a shed on the morning of February 24, 1953 There apparently was no gross evidence of injury and the man continued on his job During the day voiding was spontaneous, painless, and of normal frequency That night, however, the man was sent to the hospital, because of gross hematuria, and urological consultation solicited

The patient, who had no specific complaints and no evidence of skeletal or visceral injury associated with the fall in the morning, walked into the hospital unassisted Past history, as related by his family physician, was totally negative

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[9] McDonald, J R Exfoliative cytology in genitourinary and pulmonary diseases Am J Clin Path , 24 684, 1954

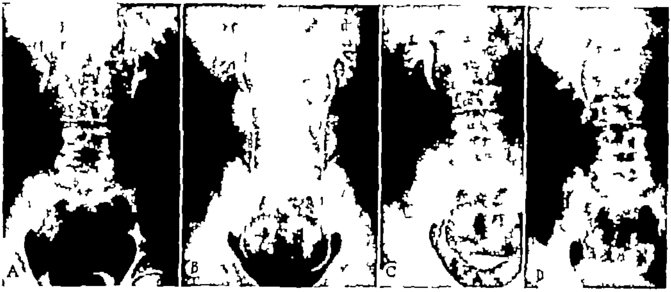

FIG 1 *A* excretory urogram taken on day of fall 15 minutes after injection of 30 per cent urokon Normal excretion bilaterally No evidence of extravasation *B*, retrograde pyelography done 24 hours following fall No demonstrable filling defects or extravasation *C* retrograde urogram of right kidney taken on tenth hospital day demonstrates no abnormality *D* retrograde pyelogram taken 24 days after fall fails to account for persistent hematuria

and unrelated to the present complaint, that of hematuria Blood pressure, pulse, respirations, and temperature were within normal range The abdomen presented no significant findings The kidneys were not palpable and both flanks were free of pain or tumefaction The bladder was not distended The perineum displayed no evidence of trauma Catheterization demonstrated an intact urethra, a smoky brown urine, no clots and, upon careful irrigation, no evidence of disruption of the bladder wall

Excretory urograms, taken immediately following the percursory physical examination, showed no deviation from normal, bilaterally Extravasation, into the renal parenchyma or out into the tissues from the drainage mechanism of the upper urinary system, was definitely absent (fig 1, *A*)

The following morning the urine persisted bloody Cystoscopy and retrograde urography revealed nothing abnormal except for bloody urine observed coming from the right ureteral orifice, which was otherwise normal in appearance The bladder mucosa was intact and normal A bleeding polyp was encountered in the prostatic urethra which was removed with biopsy forceps and the base electrofulgurated Both ureters were catheterized with ease encountering no obstruction between the bladder and the kidney pelves Bleeding from the right kidney was markedly intensified by the insertion of the ureteral catheter, much in excess of what one usually encounters incidental to a cystoscopic manipulation This finding recurred during subsequent cystoscopies The retrograde urograms were normal in every respect The smooth outline of the total drainage mechanism ruled out the possibility of trauma, stone, neoplasm, or chronic pyelonephrosis (fig 1, *B*)

The polyp regarded as a possible source of the bleeding was subsequently exonerated from all blame However, the specimen was sent for histological study and the pathologist s report stated "There is no evidence of malignant neoplastic growth "

Hematuria continued undiminished in spite of a normal hospital record and a symptomless patient On the tenth hospital day a right retrograde urogram was done without showing any demonstrable filling defect in the renal pelvis A repeat urogram 2 weeks later failed to shed any additional light on the etiology of the hematuria (fig 1, *C* and *D*)

The obvious medico-legal implications in this case made it mandatory that a definitive diagnosis be made and its relationship to the trauma incurred be established To submit a diagnosis of essential hematuria is contrary to my convictions and would not be legally acceptable With this in mind, the search for the causative factor continued

Entertaining the possibility of an angioma, on the fourteenth hospital day, the right kidney pelvis was irrigated with 1 per cent silver nitrate solution through a 7F plastic ureteral catheter which was left retained for 24 hours This procedure proved useless and the hematuria persisted unabated

On the seventeenth hospital day a 24-hour specimen of urine was sent to the laboratory with a request for study of the sediment for acid-fast micro-organisms as well as a Papanicolaou stain of the cellular elements Subsequently the pathologist reported "Acid-fast bacilli are not demonstrable The cellular elements are strongly suspicious of papillomatous growth, possibly papillary carcinoma "

To substantiate the finding of tumor cells more convincingly, the right kidney pelvis was irrigated with normal saline solution and the collected specimen sent to the laboratory for further evaluation The following report ensued "Blocks

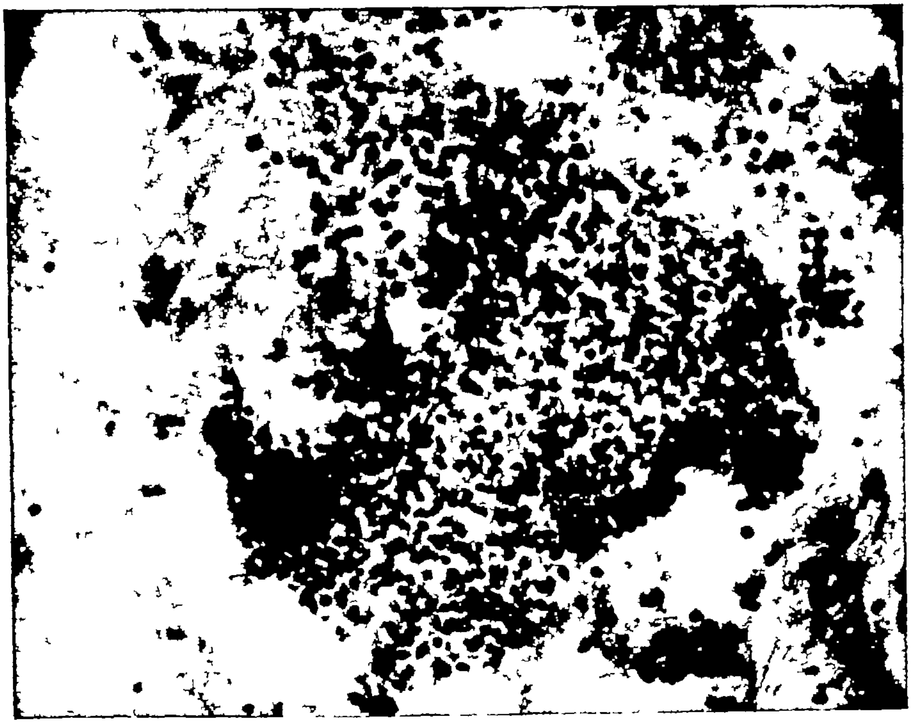

FIG 2 Clump of cells obtained by irrigating the right kidney pelvis ×250 Nuclei are hyperchromatic with noticeable variation in size and shape

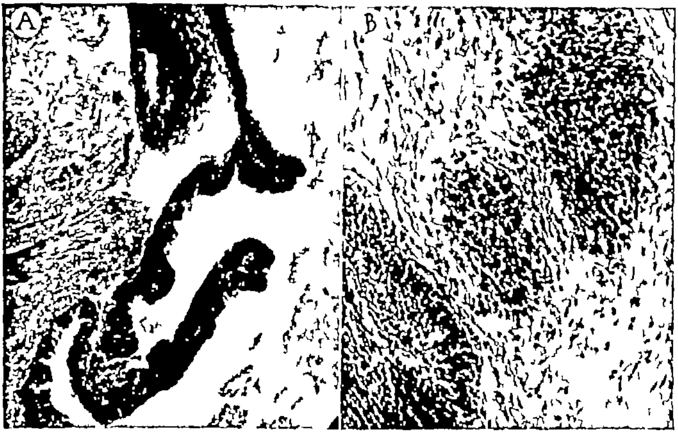

FIG 3 *A* section through papillary lesion from kidney pelvis ×85 Note thickening of lining membrane with extension of neoplasm into the submucosa *B* same as *A* ×150 Hyperchromatic nuclei with variation in size and shape are clearly visible Tumor cells extend beyond boundary of neoplasm

made from sediment obtained by irrigating the kidney pelvis show a pattern essentially resembling that seen in the previous study of the 24-hour urine Minute cell groups, resembling those described before, are more clearly observed now This strongly suggests the presence of a papillary lesion probably located in the renal pelvis" (fig 2)

After consultation with other pathologists, who concurred in the diagnosis, a right nephrectomy was performed, by the customary lumbar approach, on March 31, 1953 No difficulty was encountered during surgery A large portion of the ureter was resected along with the kidney Grossly, the organ displayed no abnormality On section, however, and after a persistent search by the pathologist, a papillary lesion, 4 mm in longest diameter, was observed in the upper major calyx The ureter appeared normal throughout its length externally as well as internally A summary of the pathologist's report reads as follows "Lesions found were limited to the mucosa of the renal pelvis in the area of grossly visible alteration In these fields the lining membrane is found to consist of 8 to 10 layers instead of the customary 2 to 5 In several fields the cell borders are indistinct and the nuclei are hyperchromatic and show slight variation in shape and size Crowding of cells with rather dark, varying sized nuclei is seen in and around the papillary protrusions There is also penetration of a few nests of abnormal cells into the immediately adjacent connective tissues The renal parenchyma as well as the vessels and the ureter are free of essential changes While the lesions observed are not too impressive, I believe that they are indicative of an early transitional cell type papillary carcinoma of the renal pelvis" (fig 3)

The postoperative course was essentially uneventful Hematuria promptly disappeared with no evidence of recurrence in over two years The patient was discharged from the hospital on the tenth postoperative day and returned to his gainful occupation three weeks after surgery

Twenty-nine months following the surgical episode, the patient was found to be in good health and, on cystoscopy, nothing abnormal was encountered in the bladder The urine was clear grossly and negative chemically as well as microscopically

## DISCUSSION

The confusing element in this case was the trauma sustained which apparently initiated the hematuria This incident was discarded as an etiological factor in the hematuria when urography was predominantly negative and when, after a reasonable period of bed rest, the bleeding persisted Infection was likewise ruled out in view of the negative pathological reports Repeated cystoscopies and retrograde urograms failed to demonstrate a lesion, a filling defect, or any other abnormality to account for the bleeding By the process of elimination the diagnostic problem was reduced to two possibilities angioma or neoplasm

In desperation, after all accepted diagnostic procedures failed to establish the etiology of the persistent hematuria, histological investigation of the cellular elements in the urinary sediment resolved the diagnostic difficulty In spite of the element of error, that is at times encountered in the histological differentiation of the tumor cell from the normal, this case demonstrates that cytology, as a laboratory procedure, is practical and an invaluable adjunct to our diagnostic armamentarium in early urinary tract neoplasms of the papillary variety

## CONCLUSIONS

A confusing problem of persistent, painless hematuria is presented

The acceptable routine diagnostic procedures failed to establish a diagnosis

The smear test applied to the cellular elements of the urinary sediment proved dependable, in this instance, and led to surgery before the neoplasm reached inoperable proportions

Cytology is a dependable diagnostic procedure and deserves more extensive exploration in its application to malignancy of the urinary tract

I am deeply grateful to Doctors Karl Neuberger and Michel Bograd for their co-operation and assistance in this case

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# BIOPSY OF THE LOWER URETER

BAXTER A SMITH JR

It is comforting to have a pathologic diagnosis support a preoperative clinical diagnosis, the pathologic diagnosis may alter the therapeutic procedure Biopsy of many lesions of the ureter may be made endoscopically These methods no doubt are used frequently but the only reference I have found to them in the literature is that of Roome, Flett, and Spooner

If a ureteral lesion is intramural or juxtavesical and the orifice will permit, biopsy may be taken with the flexible biopsy forceps

Satisfactory biopsy of lesions in the pelvic ureter, including the intramural and juxtavesical areas, may be obtained if the Johnson basket will pass them Following introduction of the basket beyond the suspected level, the bladder is emptied and the basket rotated as it is withdrawn into the bladder A small amount of irrigating fluid is used to rinse the bladder, and smears and sections of the sediment are made promptly At times, good sized pieces of tissue adequate for section are obtained Rotation of the basket must be to the right if the basket is detachable

## ILLUSTRATIVE CASES

*Case 1* Patient was followed 3 years for recurrent, superficial papillary carcinoma of the bladder and interstitial cystitis Urogram December 1948 was negative for stasis At routine check, February 1949, mucosa within right ureteral meatus looked fuzzy, flexible biopsy forceps introduced 1–2 cm and bite of tissue obtained showing transitional carcinoma with invasion (fig 1) Cystectomy was done

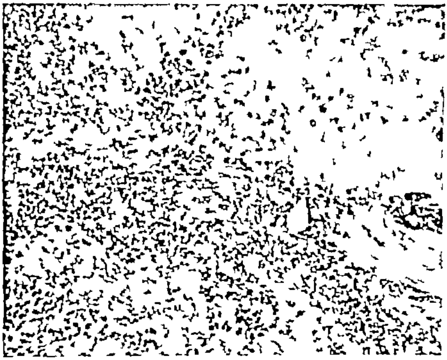

Fig 1 Case 1 Ureteral biopsy obtained with flexible biopsy forceps Note presence of muscle

Read at annual meeting of North Central Section of American Urological Association Chicago Ill September 29–October 1 1955

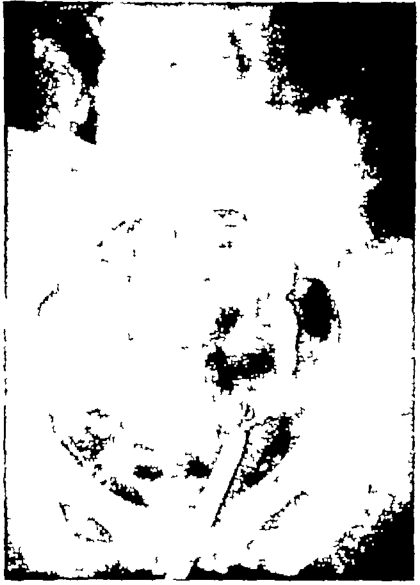

Fig 2 Case 2 Ureterogram

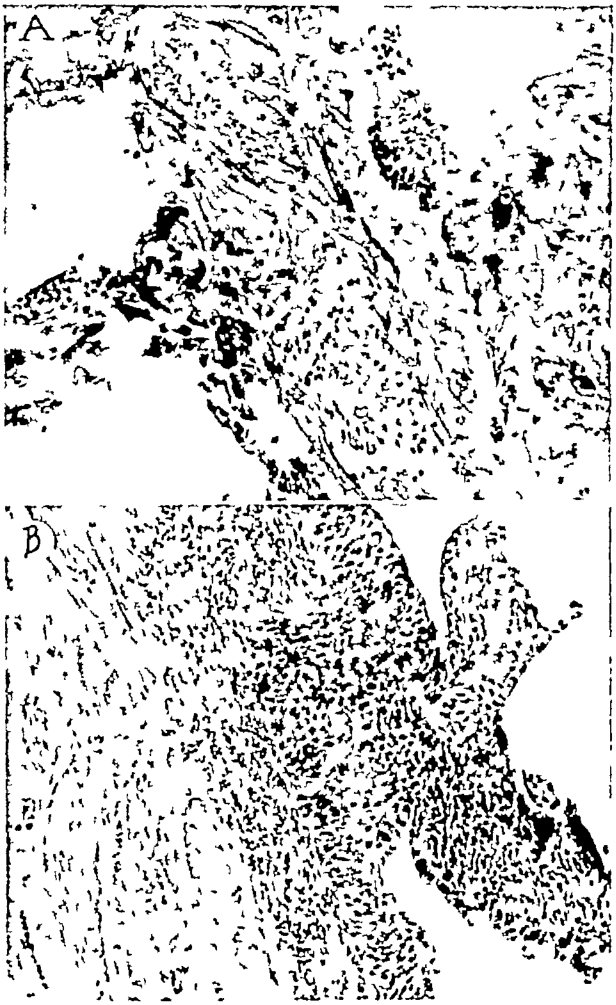

Fig 3 Case 2 A, biopsy obtained by Johnson basket, section of sediment Some submucosal tissue present *B*, section of excised ureter

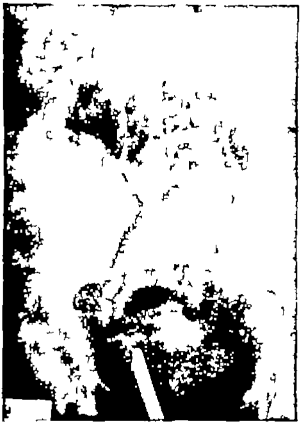

Fig 4 Case 3 Pyeloureterogram

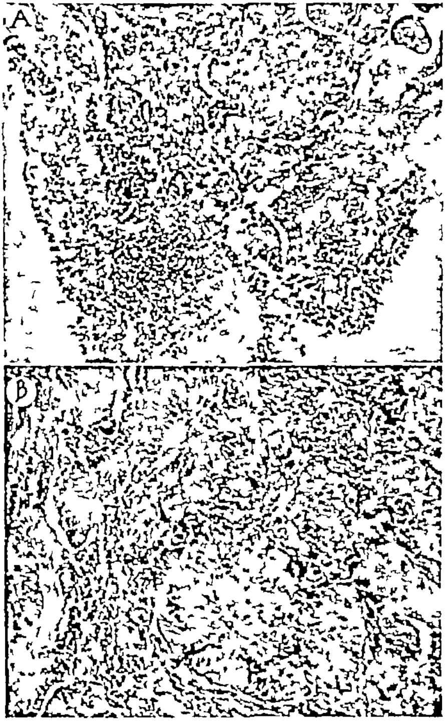

Fig 5 Case 3 A biopsy obtained by Johnson basket section of sediment *B* section of excised ureter

*Case 2* Papillary carcinoma of the base of the bladder was treated by transurethral excision and radon implantation in 1949, left ureteral orifice was excised but not grossly involved in lesion April 1951, excretory urography demonstrated left hydronephrosis, a pyeloureterogram with use of an acorn bulb showed stricture or tumor of the juxtavesical ureter (fig 2) Biopsy with the Johnson basket showed tumor (fig 3, *A*) Section of the ureter removed at nephroureterectomy with excision of bladder cuff is shown (fig 3, *B*)

*Case 3* Patient underwent vesical diverticulectomy for carcinoma involving the diverticulum in 1951 In 1952 a recurrence in the anterior wall was treated cystoscopically In October 1954, the bladder was negative, but hematuria of right upper tract origin occurred Retrograde pyelogram showed irregularity of the lower ureter (fig 4) Biopsy with the Johnson basket was done (fig 5, *A*) prior to nephroureterectomy with bladder cuff Figure 5, *B* is a section of the ureter

## CONCLUSIONS

Attention is called to two methods of biopsy for lower ureteral lesions Upper ureteral lesions might be amenable to use of the flexible loop, multiple catheters, or the nylon (Levant) basket

It is of interest that the 3 patients cited had been followed 3 years for carcinoma of the bladder before ureteral lesions (probably secondary?) appeared, demonstrating the necessity for periodic check of the upper urinary tract as well as the bladder

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# BILATERAL PERIURETERITIS PLASTICA

JAMES H HEJTMANCIK AND MORETON A MAGID

Extrinsic ureteral compression with obstruction due to a nonspecific retroperitoneal inflammatory process is an unusual entity with unknown etiology and uncertain prognosis Treatment has not been standardized because more experience is necessary before a definite plan of therapy can be advocated In all cases reported, the ureter was involved by an extrinsic retroperitoneal inflammatory process with no intrinsic stricture of the ureter itself demonstrable It is probable that mild forms are either unrecognized or not reported

In general, these cases fall into two distinct groups Eight cases have been reported in which the pathological process was a diffuse granulomatous type of inflammation which frequently extended from the kidneys to the sacral promontory and from one ureter to the other In these cases, the origin of the pathological process was apparently not in the immediate periureteral area but enveloped the ureters secondarily, as the inflammation spread In some, it was unilateral initially, however, both ureters eventually became involved At laparotomy, a distinct diffuse retroperitoneal mass was commonly found The first 2 patients were reported by Ormond in 1948 In one, the process extended from the kidney to the sacral promontory and included the ureters In the second, at operation, a flat retroperitoneal mass with indistinct lateral margins was felt covering the sacrum A case reported by Miller, Lipin, Meisel and Long revealed a firm, slightly hemorrhagic mass extending from the kidneys down over the sacrum A rubbery mass with poorly defined edges situated chiefly over the fifth lumbar body was found by Bradfield Diffuse involvement was also reported by Mirabile and Spillane as the most recent case reported

Probably of different etiology, largely because of the extent of retroperitoneal inflammation, but causing a very similar clinical syndrome is the entity designated as periureteritis plastica Ureteral involvement may be unilateral or bilateral Generally, the periureteral inflammatory process envelopes a variable segment of the ureter in a periureteral inflammatory cuff or plastic scar The inflammation is not diffuse and only the immediate periureteral area is included Four cases of unilateral periureteritis plastica were reported by Vest and Barelare They believed that possibly the ureter was secondarily involved from infections of the lower urinary tract through lymphatic spread

The dominant clinical features of all seem to be reduced health, back, loin or flank pain, unexplained anemia, and varying degrees of urinary tract obstruction Sometimes, the clinical course is that of severe, resistant pyelonephritis There may be progressive azotemia, oliguria or sudden total anuria, if involvement is bilateral Frequently, there is a history of normal pyelograms obtained one or two months previous to the actual onset of ureteral compression with hydronephrosis and hydroureter above The diagnosis is based, of course, on cystoscopy and retrograde pyelography

In this case, the diagnosis of periureteritis was entertained, but other diseases

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Read at annual meeting South Central Section of American Urological Association San Antonio Texas October 17-10 1955

such as malignant lymphoma, reticulum cell sarcoma, Hodgkin's disease and metastatic invasion could not be excluded and seemed more likely

## CASE REPORT

A 24-year-old white woman was first seen on November 6, 1953, with complaints of temperature elevation up to 101F and aching pains in the left flank and loin She dated the onset of her illness to May 1953, when she experienced moderately severe aching pain at the crest of the right ilium with burning and frequency of urination Her local physician found a moderate degree of pyuria and excretory urography was done (fig 1, *A*) Apparently, the pyuria responded to antibiotics, but the patient soon had episodes of nausea and vomiting which

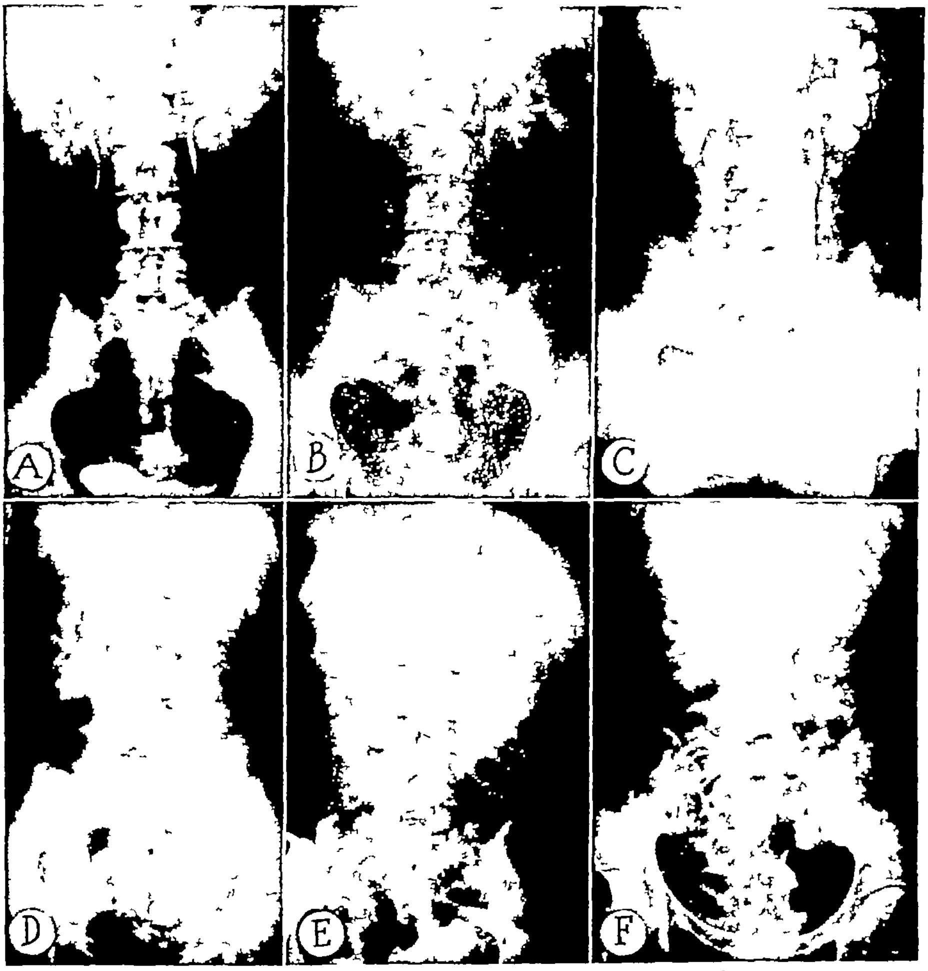

FIG 1 *A* May 1953, normal excretory urograms *B*, September 1953, excretory urograms showing early inflammatory changes *C*, November 1953, retrograde pyelograms revealing hydronephrosis and hydroureter ending at S2 *D*, April 1954, postoperative excretory urograms revealing slight improvement in the hydronephrosis on both sides *E*, October 1954, excretory urograms showing marked improvement on left side *F*, May 1955, further progression of hydronephrosis

would recur every 2 weeks accompanied by pain over the right iliac crest The episodes of nausea, vomiting and pain would last two or three days following which the patient would feel quite well and her appetite would return In July, she noted that she had daily temperature elevations sometimes as high as 102 degrees Dilatation and curettage of the uterus were done because of the possibility of an abortion with uterine infection The tissue was reported to be normal

She was hospitalized in September 1953, when her temperature was as high as 106F A thorough examination revealed no definite cause for the symptoms but it was thought most likely on the basis of a urinary tract infection Excretory urography revealed no definite abnormality (fig 1, *B*) Grade 1 pyuria was found, and cultures were reported as Pseudomonas aeruginosa and Escherichia coli She was found to be anemic and two blood transfusions were given She again responded to antibiotics and the pyuria and symptoms subsided One week later, she began having aching pain in the left flank and costomuscular angle accompanied by elevation of temperature which persisted intermittently until her next hospitalization in November She had previously received aureomycin, terramycin, streptomycin, penicillin and elkosin There had been a 50-pound weight loss during this period Her past history revealed that she had been in excellent health all of her life She had had three uneventful pregnancies, the last in August 1951

The patient was a slender woman who showed evidence of weight loss Temperature was normal on admission, although it quickly rose to 101F A complete examination revealed no significant abnormalities Microscopic examination of the urine showed from 20 to 30 white blood cells per high power field Aerobacter aerogenes was cultured from the urine A blood count revealed 2,800,000 red cells and 8 gm hemoglobin Nonprotein nitrogen was 29 mg per cent Tuberculin and coccidioidin tests were negative Cultures and guinea pig inoculation of urine and gastric washings were negative for acid fast organisms Agglutination studies for typhoid 0, typhoid A, paratyphoid A, paratyphoid B, Proteus 19 and Bacillus abortus were all negative Blood cultures were negative

An x ray of the chest revealed a small area of infiltration above the right hilum, etiology undetermined Gastrointestinal series and barium enema were normal On cystoscopy, only a mild catarrhal inflammation of the trigone was seen No 5F catheters were easily passed to each renal pelvis Retrograde pyelograms (fig 1,*C*) revealed bilateral hydronephrosis and hydroureter ending at the level of S2 Function tests with indigo carmine were normal and drainage on the 15 minute film was incomplete Following this, 10F Braasch bulb ureteral catheters were passed up each ureter without encountering an obstruction Several blood transfusions were given Subsequent x rays of the chest disclosed that the small area of infiltration had disappeared

On November 27, the abdomen was explored through a suprapubic midline incision after the ureters had been catheterized The peritoneal cavity was entirely normal The dilated ureters could be seen crossing the iliac crest retroperitoneally Just below the iliac crest, each ureter entered an area of flat in-

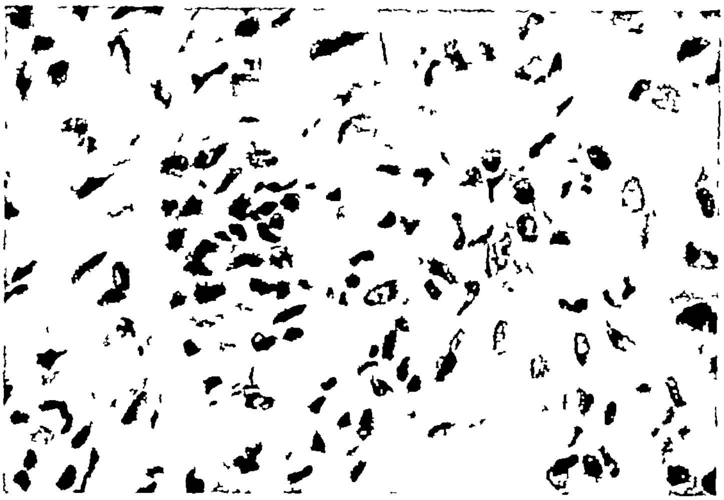

FIG 2 Periureteral plastic tissue showing areas of nonspecific inflammatory reaction

durated plastic tissue The parietal peritoneum was involved in this fibrous area The distance of involvement was approximately three centimeters longitudinally and it was localized to the immediate periureteral area Below this, the ureters were normal in appearance The peritoneum was incised and a dense plastic sheath was removed on both sides Ureterolysis was done from 1 cm above to 1 cm below the involved portion of the ureter The ureters were left free in the peritoneal cavity and the abdomen was closed A biopsy revealed localized small areas of nonspecific inflammatory reaction (fig 2)

The ureteral catheters were removed after 7 days The temperature elevation gradually subsided over a period of 2 months but the pyuria persisted despite all medication A second urine culture revealed B pyocyaneus The patient was given practically all of the urinary tract antibiotics including a trial of polymyxin B In April 1954, excretory urography revealed only slight improvement (fig 1, *D*)

The patient continued to have constant pyuria and recurrent attacks of anorexia Recovery seemed to be complicated by an understandable moderate anxiety state She complained of vague aching pains and there was no weight gain Repeated examinations revealed nothing of significance No 10F bulb catheters were easily passed to each renal pelvis

In October 1954, despite the resistant, constant pyuria, pyelograms showed marked improvement (fig 1, *E*) In May 1955, the pyuria had finally subsided, however, pyelograms again revealed some progression of the hydronephrosis bilaterally (fig 1, *F*) The patient had improved clinically, but she was still markedly underweight and complained of vague neuritic type pains in the lumbosacral area and down both legs

## DISCUSSION

Unlike most cases reported of ureteral compression from a nonspecific retroperitoneal inflammatory process, this patient is neither well nor dead Pyelography revealed marked improvement until her most recent x rays in May 1955, when the urine was free of infection for the first time in almost two years It is possible, now that the urinary tract infection has finally subsided, a slow resolution of the inflammatory process might occur It is also possible that the periureteral inflammation with compression might continue, necessitating further ureteral surgery or, eventually, bilateral nephrostomy The fact that it was impossible to eradicate the urinary tract infection is probably the reason that improvement has not been more marked

Speculation as to the pathogenesis of these unique periureteral inflammatory areas is of interest Vest and Barelare considered an ascending streptococcal periureteral infection from lower tract infection as the possible etiologic process Streptococci were not isolated on repeated urine cultures in this patient Since the lymphatics of the lower ureter anastomose with those of the bladder neck and trigone, it is possible that the etiologic process was periureteral lymphangitis secondary to cystitis and trigonitis A focus of infection in an organ outside of the urinary tract, such as the uterus, also might be the primary involvement and the bladder itself might be secondarily involved Another possibility, of course, is spread directly through the ureteral wall with only minimal inflammation of the mucosa and muscle, but plastic or hypertrophic changes in the adventitia Why the changes appeared simultaneously in both ureters at the same location in this particular patient is unknown

Treatment has not been standardized The most satisfactory results appear to have been obtained with ureterolysis by both intra and extraperitoneal approaches Nephrectomy and nephrostomy have been performed and deep x ray therapy, after surgery, was tried in one case

## SUMMARY

A case of bilateral ureteral compression with obstruction from a retroperitoneal inflammatory process of unknown etiology has been presented Although improvement occurred with bilateral intraperitoneal ureterolysis the inflammatory process has apparently continued

We wish to express our appreciation to Dr E O Bradfield, Scott and White Clinic, Temple, Texas for his help in preparing this paper

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# COMPLETE VALVE OF THE URETER CONGENITAL URETHRAL VALVES

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Valves of the urethra are commonly seen and reported On the other hand, ureteral valves of obstructive nature are encountered infrequently, and only 5 cases are reported in the literature No instance of complete ureteral valve has been described, and its presence in this case was considered worthy of record

## CASE REPORT

Baby boy C C A , R No Q-1081, was born at 7 55 a m , March 28, 1953, at the Plainview Hospital, Plainview, Texas—weight 7 pounds, 12 ounces The birth was a routine low forceps delivery that was carried out without incident

Immediately after birth, it was noticed that the infant had extensive generalized edema The abdomen was greatly distended Marked cyanosis was present The child was placed in an air lock, but effective respiratory excursions could never be initiated

The pediatrician who examined the baby 30 minutes after birth reported the condition moribund and noted only an occasional respiratory grunt The presence of a mass in the lower abdomen palpable to the level of the umbilicus was recorded A second mass, palpable in the right upper quadrant, was interpreted to be liver

Death occurred at 8 35 a m , forty minutes after birth

Laboratory data were

| | | | |
|---|---|---|---|
| RBC 3,890,000 | Differential | Polys, | 51 |
| | | Lymphocytes, | 45 |
| WBC 18,250 | | Monocytes, | 2 |
| | | Eosinophils, | 2 |
| Coomb's test, negative | Blood type | O | |
| Rh factor, positive | | | |

Autopsy Externally the baby appeared to be normal except for bluish discoloration The abdomen was distended and firm A tumor was palpable over the region of the symphysis pubis and in the right upper quadrant

The body was opened through a typical Y incision The heart was normal The right lung was completely collapsed, presumably due to the pressure exerted by a tremendously enlarged right kidney on the right thoracic cavity The left lung was almost completely collapsed and showed only small areas of aeration

The right kidney measured 15 cm in diameter and was filled with clear yellow fluid The left kidney was enlarged and measured 8 cm in diameter It was filled with clear yellow fluid The ureters were several times their normal diameter The bladder was enlarged and measured 8 cm in diameter The distance from the vesical neck to the dome was 10 cm

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Read at annual meeting, South Central Section of American Urological Association, San Antonio, Texas, October 17–19, 1955

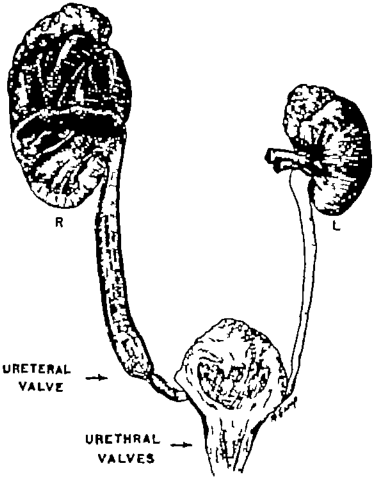

FIG 1 Note complete diaphragm of tissue across right ureter with hydroureter and hydronephrosis above

When the right kidney was opened only a hydronephrotic sac remained Little if any functioning renal tissue was present The right ureter was greatly dilated and in several locations incompletely obstructive transverse folds of mucous membrane were observed At a level 5 cm above the ureterovesical junction, a completely obstructive lesion was encountered (fig 1) Careful dissection from above and below proved this to be a diaphragm of tissue, lined with mucous membrane on its superior and inferior surfaces and completely obstructing the ureteral lumen No opening through this diaphragm could be detected

The left ureter was dilated, but completely patent through its entire length The left renal cortex showed compression atrophy due to hydronephrosis, but 50 per cent of the functioning renal tissue was estimated to remain on that side The bladder wall was grossly thickened, and grade 4 trabeculation with cellule and diverticula formation was noted The vesical neck and posterior urethra were dilated From the proximal border of the verumontanum two longitudinal valve like structures extended along the urethral floor laterally to either side of the vesical neck

The remainder of the autopsy was negative

Anatomic diagnoses Complete ureteral valve right, urethral valves, type 2, dilatation, and trabeculation of urinary bladder, hydronephroses, bilateral, secondary to ureteral and urethral valves, atelectasis, bilateral

The immediate cause of death in this infant was anoxia due to bilateral pulmonary atelectasis In all probability, proper expansion of the lungs was interfered with by the increased intra abdominal pressure and diaphragmatic elevation occasioned by two abdominal tumors

If normal respiration had occurred, it is believed that with proper management, enough renal tissue remained on the left side to support life

## DISCUSSION

Congenital valves of the urethra were first described in the literature in 1717 when Morgagni noted a case at autopsy By 1949, McCrea[1] was able to find 204 cases reported in the literature and expressed the belief that the condition was not as infrequent as the number of cases would indicate

Hugh Young first recognized the lesion cystoscopically in 1912 The following year he carried out successful surgical endoscopic removal of the valves

These valves were described as cusplike folds of mucous membrane running in the posterior urethra and usually attached to the verumontanum Young classified them into three groups, according to their relation to the verumontanum

Type 1 Those that extend from the distal border of the verumontanum, to the lateral urethral walls

Type 2 Those that extend from the proximal border of the verumontanum to the bladder neck

Type 3 An incomplete diaphragm which may lie either proximal or distal to the verumontanum

The embryology of these valves has not been definitely established, but four theories are commonly advanced

1) The Tolmatschew theory The valves are merely enlargements of ridges normally present in the urethra (This would account for only type 1 and type 2 )

2) Bazy theory The valves are due to persistence of the urogenital membrane

3) Lowsley theory The valves are due to anomalous development of the wolffian and mullerian ducts

4) Watson theory The valves are due to an attachment or fusion of the colliculus to the urethral roof

The embryology of ureteral valves is not so readily explained Transverse folds in the ureteral mucosa occur in about 5 per cent of the ureters of the newborn These are vestigial remnants which disappear early in life and are not considered to be obstructive

It is known that in the 12 mm embryo, an epithelial spur appears on the cranial side of the primary excretory duct and extends downward, closing off the lumen of the ureteric bud This is known as Chwalla's membrane, and persists until the 30 mm stage, at which time metanephric urinary excretion begins, and the membrane is ruptured by pressure necrosis Failure of this membrane to rupture might explain the case reported here, but such an explanation would not account for valves located at higher levels in the ureter

In the case reported by Wall and Wachter, an iris-like membrane was present in the distal 2 cm of each ureter These membranes contained minute openings for the passage of urine Their patient died despite surgical resection of the valves In addition to this one case, they were able to find four additional reports of ureteral valve in the literature and have described each separately In each of these cases, partial obstruction to the egress of urine was present, but in no instance was complete ureteral obstruction observed

The most valuable asset in the diagnosis of urethral valves is a constant awareness of their existence These children commonly void with a poor stream and urination may be painful or difficult Dribbling or incontinence may be present In many infants with congenital valves of the urethra, the bladder will be palpated as a tumor mass in the lower abdomen If the obstruction has existed sufficiently long, urinary tract infection and renal insufficiency may be present This diagnosis should be considered in any infant with unexplained gastrointestinal symptoms who failed to gain weight or grow properly

Once suspected, the diagnosis is readily confirmed by endoscopic visualization of the valves The posterior urethra proximal to the valves is commonly dilated and the bladder will often show such obstructive changes as trabeculation and cellule formation

Upper urinary tract obstruction and damage must be assessed by excretory or retrograde urography

Surgical correction of these obstructive lesions should be carried out following established urologic principles Frequently, endoscopic or transurethral resection of these valves can be accomplished successfully Recently Burns and others have employed open surgical exposure of the bladder neck and posterior urethra by the retropubic approach with excellent results

## SUMMARY

A case of a complete valve of the right ureter associated with type 2 urethral valves is presented

The embryology, diagnosis and treatment of ureteral and urethral valves are briefly reviewed

I wish to thank Dr R K Williams, Department of Obstetrics, Plainview Hospital and Clinic Foundation, for securing the autopsy and calling attention to the unusual findings

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Wall B and Wachter H E J Urol 68 684-690 1952

If normal respiration had occurred, it is believed that with proper management, enough renal tissue remained on the left side to support life

## DISCUSSION

Congenital valves of the urethra were first described in the literature in 1717 when Morgagni noted a case at autopsy By 1949, McCrea[1] was able to find 204 cases reported in the literature and expressed the belief that the condition was not as infrequent as the number of cases would indicate

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In the case reported by Wall and Wachter, an iris-like membrane was present in the distal 2 cm of each ureter These membranes contained minute openings for the passage of urine Their patient died despite surgical resection of the valves In addition to this one case, they were able to find four additional reports of ureteral valve in the literature and have described each separately In each of these cases, partial obstruction to the egress of urine was present, but in no instance was complete ureteral obstruction observed

TABLE 1 *Clinical data*

| Case | Epidemic | Age | Sex | Site of Paralysis | Duration of Illness at Onset of Bladder Paralysis Days | Duration of Urinary Retention Days | Residual Urine Volume cc | Treatment |
|---|---|---|---|---|---|---|---|---|
| 1 C T | 1949 | 2 | F | Arm leg | 10 | 1 | | Voided spontaneously |
| 2 D P | 1952 | 3 | F | Leg | 5 | 2 | 120 | Single catheterization urecholine |
| 3 C I | 1949 | 3 | F | Legs | 6 | 1 | | Suprapubic expression of bladder |
| 4 D H | 1949 | 3 | F | Arms abdominals, legs | 3 | 3 | | Furmethide |
| 5 C B | 1949 | 4 | F | Nonparalytic | 8 | 3 | | Furmethide hot packs |
| 6 R M | 1949 | 5 | M | Legs | 10 | 10 | Not recorded | Furmethide catheterized twice |
| 7 R U | 1949 | 5 | M | Shoulder, abdomen legs | 12 | 5 | | Furmethide hot packs |
| 8 C R | 1949 | 12 | F | Arms legs | 4 | 7 | Not recorded | Furmethide catheterized once |
| 9 R C | 1952 | 15 | M | Diaphragm, intercostals arms abdominals legs | 0 | 4 | 550 | Indwelling 16F catheter |
| 10 R S | 1952 | 17 | M | Arms legs | 6 | 5 | 300 | Indwelling 16F catheter |
| 11 J W | 1952 | 27 | M | Encephalitis, cranial nerves diaphragm intercostals arms abdominals legs Died | 3 | — | 300 | Indwelling 16F catheter |
| 12 W H | 1952 | 20 | M | Diaphragm intercostals arms abdominals legs | 5 | 23 | 900 | Indwelling 16F catheter |
| 13 M D | 1952 | 32 | M | (Same as No 11 died) | 4 | — | 750 | Indwelling 16F catheter |

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# A CLINICAL STUDY OF THE MOTOR PARALYTIC BLADDER IN POLIOMYELITIS

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Urinary retention has been reported as occurring in 4 to 42 per cent of patients with poliomyelitis in five epidemics upon which reports are available[1–5] In spite of the relative frequency of the complication there is little material in the literature upon which to base an understanding of the physiologic disturbances which occur With this consideration in mind clinical data have been collected and analyzed from 13 cases Six of the patients were observed by the author, the records of the other 7 were made available through the kindness of Dr Edward C Curnen Urinary retention was found in 13 of 117 hospitalized cases observed in the present study, an incidence of 11 per cent

## MATERIAL

The patients were seen during two epidemics one in southern New England in 1949 and one in eastern Maine in 1952 Table 1 indicates that the bladder paralysis occurred during the acute, febrile phase of the illness Among the 6 cases personally observed in 1952, urinary retention appeared concurrently with somatic paralyses in 3 patients, a day before appearance of skeletal muscle paralysis in 2 patients, and 4 days after the first skeletal muscle paralysis in 1 Distinct evidence of ileus was seen simultaneously with urinary retention in 5 of the 6 patients In all the patients (cases 9–12) who were able to report their subjective reactions, the urinary retention was accompanied by mild to severe desire to void and suprapubic distress No interference with bladder sensation was apparent In the younger patients and in one of the adults (case 13) who had severe encephalitis, bladder distention, usually accompanied by overflow incontinence, were the usual presenting signs Large residual urine volumes

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Acknowledgements Dr Edward Curnen, professor of pediatrics, University of North Carolina School of Medicine, has permitted inclusion of certain patients under his care in the study Dr Clyde Deming, professor emeritus of urology, Yale University School of Medicine, Dr Derek Denny Brown, professor of neurology, Harvard Medical School, and Dr Reed Nesbit, professor of urology, University of Michigan, have advised in their fields of special interest, during various stages of the study Dr H E MacMahon, professor of pathology, Tufts University School of Medicine, reviewed the microscopic sections

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| 8 C R | 1949 | 12 | F | Arms legs | 4 | 7 | Not recorded | Furmethide catheterized once |
| 9 R C | 1952 | 15 | M | Diaphragm intercostals arms abdominals legs | 0 | 4 | 550 | Indwelling 16F catheter |
| 10 R S | 1952 | 17 | M | Arms legs | 6 | 5 | 300 | Indwelling 16F catheter |
| 11 J W | 1952 | 27 | M | Encephalitis cranial nerves diaphragm intercostals arms abdominals, legs Died | 3 | — | 300 | Indwelling 16F catheter |
| 12 W H | 1952 | 29 | M | Diaphragm intercostals arms abdominals legs | 5 | 22 | 990 | Indwelling 16F catheter |
| 13 M D | 1952 | 32 | M | (Same as No 11 died) | 4 | — | 750 | Indwelling 16F catheter |

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# THE LOWER URINARY TRACT IN TREATED NEUROSYPHILIS

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Bladder dysfunction has been reported to occur in a significant number of patients with neurosyphilis [1 3] According to present concepts, degeneration of the posterior roots of the spinal nerves resulting from the disease leads to impairment of proprioceptive sensation from the bladder [4 5] Failure to appreciate filling of the viscus results in over-distension which eventually damages the detrusor so that hypotonia and even varying degrees of urinary retention occur

The dermatology and neurology departments of the Hospital of the University of Pennsylvania have treated and followed a large group of tabetic patients for many years, but these patients were rarely encountered in the urology clinic This study was initiated to evaluate the urologic status of this group of treated tabetics

## MATERIAL AND METHODS

Forty-one patients with proven tabes dorsales or taboparesis were selected at random from the dermatology and neurology clinic files Every patient had received penicillin therapy for neurosyphilis Some had previously been treated with other antiluetic agents Thirty-three of the group were male, and eight female The mean age was 52 9 years

The evaluation of each patient included a personal history, with careful attention to urologic symptoms, physical examination with emphasis on the neurologic investigation, urethrocystoscopy and cystometry Endoscopy was performed without anesthesia Intravesical obstruction was graded from "not present" to "4 plus " The continuous recording cystometer as described by Milam and Leberman[6] permitted analysis of bladder sensation and provided a graphic record of intravesical pressure while the viscus filled and when the patient tried to void

## RESULTS

The 41 patients were divided into three groups (table 1) Group 1 contained 18 patients (43 8 per cent) who demonstrated impaired proprioceptive sensation from the bladder Increased capacity (> 550 ml in males and > 650 ml in females)

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Read at annual meeting, Northeastern Section of American Urological Association, Lake Placid, N Y September 22-24, 1955

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Emmett, J L and Beare, J B J A M A, **117** 1930-1934, 1941

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[6] Milam O F and Leberman, P R J Urol, **66** 597-602, 1951

TABLE 1 *Results of urologic evaluation*

| | Group 1 (Proprioception ↓) | Group 2 (Other ves. dysfunction) | Group 3 (Normal) |
|---|---|---|---|
| *Patients* | | | |
| No and % of | 18 (43.8%) | 9 (22%) | 14 (34.2%) |
| *Obstruction* | | | |
| + | 7 | 2 | 3 |
| ++ to ++++ | 7 | 5 | 0 |
| Total | 14 | 7 | 3 |
| *Residual Urine* | | | |
| 30–60 ml | 1 | 3 | 0 |
| 60 ml | 7 | 4 | 0 |
| Total | 8 | 7 | 0 |
| *Symptoms* | | | |
| Incontinence | 5 | 1 | 0 |
| Any | 7 | 4 | 1 |

and/or delayed first desire to void (>350 ml) were considered evidence of decreased proprioception. Group 2 contained 9 (22 per cent) patients who had apparent dysfunction of their urinary tract without evidence of impaired sensation. Group 3 contained 14 (34.2 per cent) patients whose bladder function seemed relatively normal.

Infravesical obstruction of some degree was noted in 24 of 41 patients (58.5 per cent). Fourteen of 18 patients (77.8 per cent) in group 1 had some increase in the resistance to urinary outflow. It was mild in 7 and moderate to marked in 7. Seven of 9 patients (77.8 per cent) in group 2 had obstruction which was moderate to marked in 5 and mild in 2. Thus, of those with bladder dysfunctions (groups 1 and 2) 21 of 27 persons (77.8 per cent) had some element of infravesical obstruction present. Only 3 of 14 (21.5 per cent) of those with normal bladder function (group 3) exhibited obstruction and it was usually of mild degree when present.

Residual urine of 30 ml or more was found in 15 of 41 patients (36.6 per cent). Sixty ml or more was found in 11 of 41 (26.9 per cent). Some degree of infravesical obstruction was noted in all but one of those with residual urine. It should be noted that only 3 of the 11 and 4 of the 15 just mentioned complained of urinary tract symptoms.

Urinary tract symptoms were present in 12 of 41 patients (29.3 per cent). All but one of those with urinary tract symptoms were in groups 1 and 2 (those with objective evidence of bladder dysfunction).

Some form of poor voluntary urinary control (enuresis, postvoiding dribbling, frank incontinence, etc.) was present in 6 of 41 patients (14.6 per cent). Five were in group 1 and 1 was in group 2. No patient had any marked incontinence. Only 1 with poor control (patient 17, enuresis) had a large amount of residual.

Tabetic pains were complained of by 11 of 18 patients in group 1 (decreased proprioception) while only 4 of 23 patients in groups 2 and 3 were so afflicted.

No definite relationships could be established between impaired bladder proprioception and 1) the severity of the neurosyphilis as determined by physical examination, 2) the known duration of the central nervous system lues, or 3) the cerebrospinal fluid findings and blood serology

## DISCUSSION

Obstruction appears to have played an important part in the vesical dysfunction of the patients in this study Infravesical obstruction was usually the sole cause of bladder dysfunction in group 2 (intact sensation) and commonly a contributing cause of vesical dysfunction in group 1 (decreased proprioception) Obstruction occurred in 77 8 per cent of both groups with bladder malfunction (1 and 2) but obstruction was more often severe in group 2 (intact sensation) than in group 1 Obstruction was noted in only 21 5 per cent of those with normal vesical function Furthermore all but one of those carrying significant residual urine had increased resistance to urinary outflow The importance of obstruction in vesical dysfunction among tabetics has been stressed by Emmett[2, 7] In fact, the reduction of outflow resistance by surgery is often the therapy of choice for tabetic patients with marked aberrations of vesical function[2, 7]

Residual urine of 60 ml or more was found in 26 8 per cent of the patients However, only 27 3 per cent of those with residual urine had symptoms referable to the urinary tract These findings point out the need to determine residual urine in every tabetic patient irrespective of the presence or absence of urinary symptoms

Some evidence of decreased proprioceptive sensation from the bladder was found in about 43 per cent of the patients Either tabes or obstruction can cause the impairment of bladder sensation The degree to which each contributed to the vesical dysfunction of individual patients in group 1 varied greatly Brodie et al[3, 8] performed cystometry in a group of asymptomatic neurosyphilitics (not tabetics) who had no urinary tract symptoms and no residual urine Every patient had received "adequate" antiluetic therapy with heavy metals Some evidence of diminished proprioceptive sensation from the bladder was found in about 67 per cent of the patients It is possible that even more patients would have demonstrated impaired bladder sensation if tabetics, selected at random (including those who might have had urinary symptoms or residual urine), had been studied instead of asymptomatic neurosyphilitics

Symptoms referable to the urinary tract were noted by 29 2 per cent of the patients in this study The incidence of urinary symptoms in tabetic patients had been reported in the literature as close to 50 per cent[1, 2] Approximately 14 8 per cent of the patients in this study complained of some form of poor voluntary urinary control O'Leary et al,[9] in a co-operative study, reported some form of incontinence in 34 per cent of untreated tabetic patients Following therapy with heavy metals 25 8 per cent still had some degree of urinary incontinence

Emmett, J L and Beare, J B J A M A, **136** 1093–1096, 1948

[8] Brodie, E I, Helfert, I and Phifer, I A J Urol, **43** 496–510, 1940

[9] O'Leary P A, Cole, H N, Moore, J E, Stokes, J H, Wile, U J, Parran, T, Vanderlehr, R A and Usilton, L J Ven Dis Inf, **19** 367–396, 1938

TABLE 2 *Results from neurologic examinations*

| Patients with | Group 1 (18) (bladder sensation ↓) | Groups 2 and 3 (23) (bladder sensation normal) |
|---|---|---|
| Tabetic pains | 11 | 4 |
| Ataxia | 11 | 0 |
| Pupillary changes | 18 | 20 |
| Tendon reflex changes | 15 | 22 |
| Position sense ↓ | 6 | 4 |
| Vibration sense ↓ | 0 | 8 |

It appears that vesical dysfunction and urinary tract symptoms occur less frequently in tabetics treated with penicillin than among those either untreated or having received heavy metal therapy

The frequent occurrence of "tabetic or lightning" pains in patients with bladder disturbances and neurosyphilis had been previously reported by Caulk[10] This study demonstrates that tabetic patients with impaired bladder sensation are far more likely to have experienced ‘tabetic" pains than those tabetics with intact vesical sensation No other relationships between the neurologic evaluation and vesical dysfunction could be found (table 2)

## CONCLUSIONS

The baseline evaluation of every tabetic patient should include a residual urine determination

Infravesical obstruction is commonly found in those tabetic patients with vesical dysfunction Obstruction is usually an etiologic factor in this dysfunction

Penicillin antiluetic therapy seems to have reduced the incidence of vesical dysfunction and urinary tract symptoms in tabetic patients

Tabetics with decreased bladder proprioceptive sensation are more likely to suffer from tabetic or lightning ’ pains than tabetics with unimpaired bladder sensation

[10] Caulk J R and Greditzer H G Am J Syph 1 42 1917

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# PERINEAL SIGMOIDOSTOMY IN CASES OF TOTAL CYSTECTOMY

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Urinary diversion by means of a ureterosigmoidostomy is plagued by three major complications If the various technical measures designed to prevent reflux are applied, obstruction usually ensues If an open mucosal method is used, there is danger of fecal reflux Hyperchloremic acidosis is a frequent complication of urinary diversion into the enteric tract,[1] whether due to absorption of urinary chlorides,[2] or to primary renal damage [3] Boyce and Vest[4] suggested separation of the fecal and urinary stream by ureterorectal anastomosis and abdominal colostomy in the treatment of bladder exstrophy It is well known that when urine enters an intact large bowel, reflux may occur as far as the cecum, passing over a large mucosal surface and thus being easily absorbed Pressure in the intact sigmoid may rise from 170 to 280 cm of water on defecation, whereas the voiding pressure in the isolated rectum will stay below 30 cm of water [5] By separating the fecal and urinary streams, a smaller resorptive area is presented to the urine and reflux of fecal material into the renal pelves avoided With these factors controlled, a mucosa-to-mucosa ureterorectal anastomosis prevents obstruction to the ureters These principles have been applied in treatment of carcinoma of the bladder in the adult [6-8]

Lowsley, Johnson and Rueda[9] have described a method of implanting the ureters into a closed stump of intact rectum which thereafter functions as the bladder The severed end of the sigmoid is pulled through the dilated anal sphincter anterior to the rectum so that both urinary and fecal openings are under voluntary control[10] (figs 1 and 2)

The purpose of this paper is to report our experience in 5 patients in whom this procedure has been performed

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Read at annual meeting, South Central Section of American Urological Association, San Antonio, Texas, October 17–19, 1955

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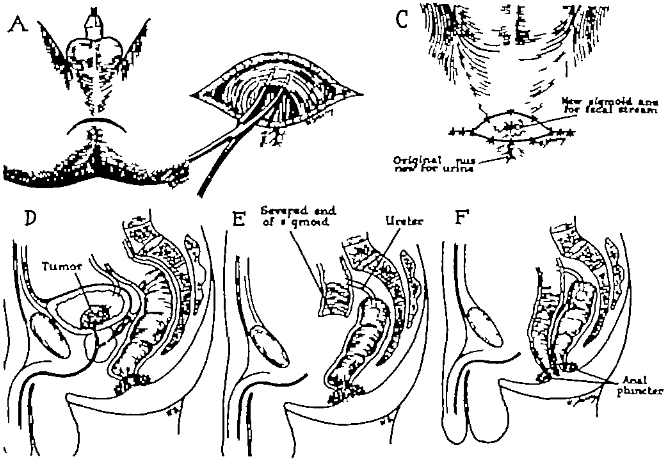
A
C
New sigmoid anus for fecal stream
Original anus now for urine
D
Tumor
E
Severed end of sigmoid
Ureter
F
Anal sphincter

FIG 1 *A*, perineal incision as if for perineal prostatectomy *B* sphincter muscle of anus is freed up and pelvis entered *C D E F* sigmoid brought through anteriorly to anus under sphincter muscle and sutured to skin with moderate protrusion

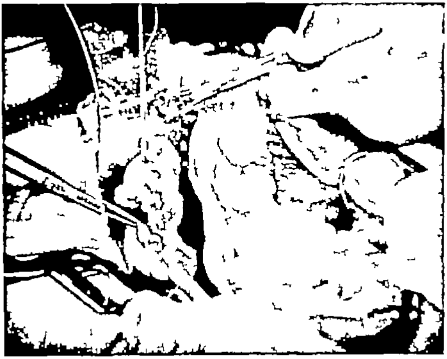

FIG 2 Rectum closed and held in place by sutures Sigmoid mobilized and held up by bowel clamp and left ureter held with thumb forceps ready for mucosa to mucosa anastomosis

## CASE REPORTS

*Case 1* A 54 year old white man was admitted to the hospital in June 1954 having passed blood clots and tissue in his urine during the preceding 2 weeks He had had a long standing stricture of the urethra and a previous diagnosis had been made of latent neurosyphilis A carcinoma of the lip had been removed several years earlier Cystoscopy and biopsy revealed a squamous cell carcinoma of the left bladder base surrounding and obscuring the left ureteral orifice

On July 1, 1954, a total cystectomy was performed together with a pelvic lymphadenectomy, ureterorectal anastomosis by the open mucosa-to-mucosa technique, and a perineal sigmoidostomy The procedure required 7 hours' operating time Pathologic examination revealed an infiltrating squamous cell carcinoma of the bladder with involvement of the perineural lymphatics and complete replacement of one lymph node adjacent to the tumor

The patient's immediate postoperative course was uneventful, urinary and fecal control developed and he was discharged from the hospital

On the eighty-fourth postoperative day, he was readmitted to the hospital with signs of acute peritonitis An exploratory laparotomy disclosed an abscess in the left lower quadrant that was drained Because it was believed that the abscess might have been associated with leakage from the sigmoid, a loop colostomy was performed In retrospect, it seemed that this was probably not the case, since x-ray study of the sigmoid showed it to be intact A more likely explanation was incomplete pelvic drainage at the original operation on July 1, 1954, despite the use of a perineal Penrose drain After the removal of this drain, a 50 cc irregularly shaped, perirectal cavity existed and was subsequently transformed into a closed space by closure of the overlying perineal skin This was the site of the subsequent abscess formation

One more complication developed in the form of a small bowel obstruction which was relieved by surgery on October 6, 1954 Despite this stormy course, he finally recovered and was discharged from the hospital in January 1955, with the ureterorectal anastomosis intact and with an abdominal colostomy

Fifteen months postoperatively, excretory urography was unchanged from the preoperative film (fig 3) The rectogram showed left ureteral reflux when maximal rectal distention was instituted (fig 4) Urinary continence could be maintained if urinary evacuation was performed at 2-hour intervals In spite of

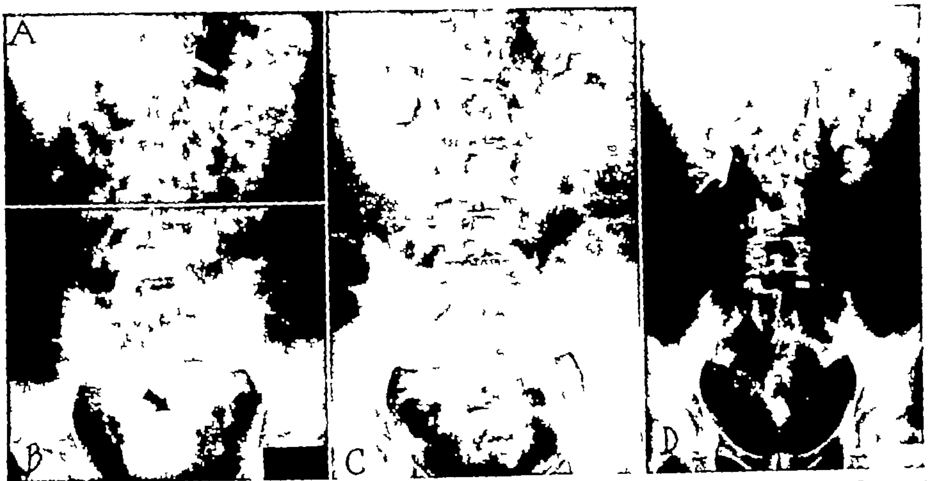

FIG 3 Case 1 A, B, preoperative excretory urogram C, excretory urogram 2 months postoperatively D, 15 months postoperatively

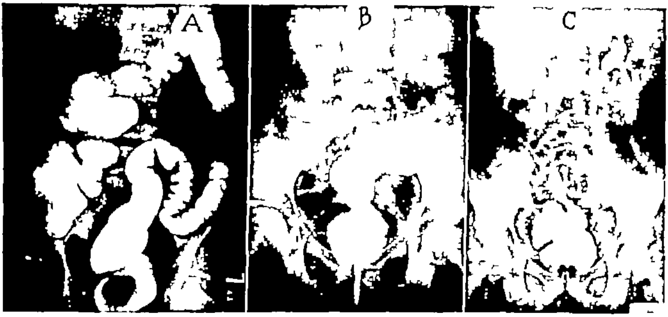

FIG 4 Case 1 *A* preoperative barium enema *B* rectogram 2 months postoperatively *C* rectogram 15 months postoperatively with reflux on left side

periodic alcoholic bouts, he maintained his position as a cook Blood chemistries at that time were as follows Urea nitrogen 18 mg per cent, $CO_2$ 18 6 mEq/l, chlorides 113 mEq/l, sodium 139 mEq/l, potassium 4 9 mEq/l, hematocrit 45 per cent The rectal urine has continued to contain Escherichia coli, with mucus and pus cells present One attack of left pyelonephritis followed the rectogram study

*Case 2* A 59 year-old white man had hematuria for 6 months prior to hospitalization Cystoscopy and biopsy revealed a large transitional cell carcinoma and on December 29, 1954, a total cystectomy, ureterorectal anastomosis, pelvic lymphadenectomy and perineal colostomy were performed The elapsed operating time was 7 hours Pathologic examination revealed an infiltrating transitional cell carcinoma with metastasis in one obturator lymph node

At operation, the peritoneal floor was preserved and carefully repaired before closure of the abdomen On the thirtieth postoperative day an intestinal obstruction developed, laparotomy disclosed that the obstruction was due to firm adhesions of the small bowel to the pelvic peritoneum without disruption of the peritoneal floor or herniation A plication procedure was performed and the patient recovered He was discharged from the hospital in March 1955 with fair control of urine and feces

The patient did poorly at home and was readmitted to the hospital in May 1955 because of diffuse spread of his carcinoma He died on June 8, 1955, six months after the original surgery Autopsy showed diffuse carcinoma with involvement of the pelvis, ureters, liver and skin

*Case 3* A 60 year-old white man had symptoms of dysuria, hematuria, and nocturia in May 1954 A bladder tumor was discovered in June, but the patient procrastinated and it was not until August 1954 that a biopsy was performed, the report was an unusual type of adenocarcinoma of the bladder

The patient at first refused surgery and was given deep x ray therapy 7,800 r through four portals to the bladder area from September 27 to November 26 1954 His symptoms progressed and on subsequent biopsy, no change could be seen in the tumor cystectomy and this is borne out by the fact that three of these 5 patients had lymph node involvement If this procedure is to be done, the whole operation must be performed at one stage and cannot be done in successive steps

## SUMMARY

The cases of 5 patients with carcinoma of the bladder have been presented in which total cystectomy has been performed together with pelvic lymphadenectomy, ureterorectal anastomosis, and perineal sigmoidostomy The functional results have been sufficiently encouraging to warrant further trial of this procedure

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catgut Suprapubic cystostomy was performed in the usual manner The patient received 1,500 cc of blood and was returned to bed in good condition

The postoperative course was uneventful The highest temperature elevation was 102 5F on the third day The patient was discharged October 28, 1953 (nine days postoperatively) with an indwelling suprapubic catheter in place

The patient was readmitted to the hospital in December 1953 (forty nine days after injury) for attempt of construction of perineal urethra with split thickness skin graft

Under spinal anesthesia the old suprapubic cystostomy incision was reopened and a 24F sound passed antegrade through the vesical neck into the perineum, which was incised over the point of the sound The perineal incision was lengthened, dissecting the muscles laterally on each side and the urogenital diaphragm exposed A 18F caliber polyethylene tube was passed through the opening into the bladder This was anchored in place inside the bladder by tying a knot in the tubing A plastic surgeon obtained a split-thickness graft, 015 inches thick, with the Brown electrotome from the essentially hairless area of the pectoral area The skin was turned inside out and fashioned into a tube over a 24F sound using 0000 chromic catgut for suture material This tube was placed over the polyethylene tubing and anchored in place to the inferior portion of the urogenital diaphragm with the same suture material The perineal muscles were pulled together around the split-thickness graft with interrupted 000 chromic catgut A 00 braided wire suture was passed through the skin and polyethylene tube, anchoring it in place in the perineum The bladder was closed around a No 24 Foley catheter in the usual manner followed by closure of fascia and skin

Minimal infection occurred around the graft and the perineum The highest temperature was 101F, gradually returning to normal Penicillin and streptomycin were administered daily The patient was discharged on December 20, 1953 (thirteen days after construction of perineal urethra)

The patient was readmitted to the hospital January 24, 1954 (six weeks after urethral construction)

Pentothal sodium and nitrous oxide anesthesia was administered A No 18 Foley catheter was sutured to the splinting polyethylene tube in the perineal urethra The suprapubic tube was removed Through the cystostomy opening a curved clamp was passed into the bladder grasping the knotted polyethylene tube removing it from the bladder and pulling the No 18 Foley catheter into the bladder by way of the newly formed urethra This urethral catheter was left indwelling The suprapubic fistula was closed The patient was discharged from the hospital January 30, 1954 (six days after last admission), with a urethral catheter in place

The urethral catheter was removed February 13, 1954, six weeks after the operation, to construct the perineal urethra Urethral dilatations at 2 week intervals were progressively lengthened to intervals of 3 months at present time Mild contracture of the skin edge was present but this can now be dilated to 24F with ease Complete urinary control is present. The urine was free of infection three months after removal of indwelling catheter

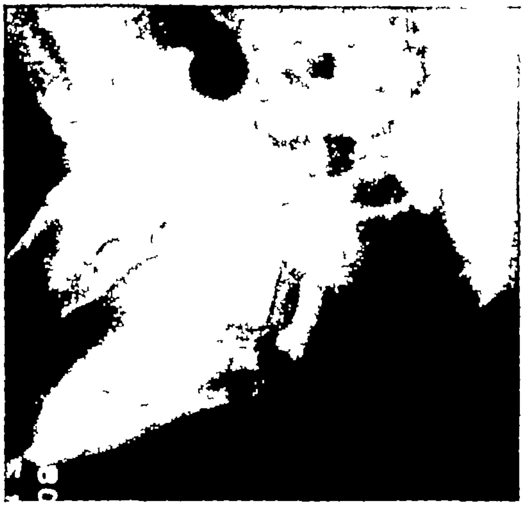

FIG 1

*Case 2* A 63-year-old Negro was admitted to the hospital February 2, 1954, complaining of a mass in the perineum of 2 weeks' duration Three months earlier he had presented himself to his local doctor because of urethral discharge and dysuria He gave no prior history of venereal disease, stricture, obstructive symptoms or hematuria Dilatation of the urethra by passage of sounds at least once each week afforded some relief The sudden appearance of the mass which increased rapidly in size caused him to enter the hospital

Physical examination was normal except for a 6 cm mass in the perineum extending into the scrotum It seemed to incorporate the urethra and was fixed, hard, nodular and painless A constant purulent discharge exuded from the meatus There was no adenopathy and no evidence of disease involving any other system of the body

Laboratory studies Urine contained 4–6 red blood cells, 4–6 white blood cells, trace of occult blood, otherwise negative White blood count 10,500 with normal differential Hemoglobin was 13 5, hematocrit 45, sedimentation rate 35 and nonprotein nitrogen 37 VDRL was positive, Kolmer complement fixation negative Chest x-ray was normal Excretory urogram was normal Urethrogram showed filling defect in the bulb with extravasation consistent with carcinoma of the urethra (fig 1)

Attempts to pass sounds through the urethra were unsuccessful Endoscopy revealed a red, hemorrhagic, friable mass in the bulbous portion of the urethra from which a biopsy was taken The tissue removed was consistent with squamous cell carcinoma of urethra There was no evidence of local or distant metastases, and the patient was considered a candidate for radical surgery

Under general anesthesia the patient was placed in lithotomy position, prepared and draped for complete excision of the penis Incision was made around the base of the penis and extended posteriorly through the median raphe of the scrotum After the scrotum was bivalved a complete excision of the penis and mass including the bulbous urethra was accomplished In order to completely remove the tumor, it was necessary to detach the urethra at the triangular ligament There was insufficient urethra to bring out the perineum to serve as a permanent perineal urethrostomy A plastic surgeon using a Brown electrotome secured a split thickness graft measuring 015 inches in thickness from the upper left pectoral area where there was a minimum of hair Over a 30F sound this graft was inverted into a tube measuring approximately three inches in length and 12 to 15 mm in diameter The graft was sutured to the membranous urethra with four sutures of 0000 chromic catgut and was splinted with an 18F polyethylene tube The distal end of the graft was brought out through a stab wound in the perineum and was attached to the skin margins with 0000 chromic catgut sutures About 1 5 cm of the graft protruded from the skin surface No attempt was made to close the superficial perineal tissue snugly around the graft Urinary stream was diverted by cystostomy

The patient's postoperative course was uneventful There was sloughing of the tube graft in the perineum external to the skin On March 30, after the graft had been splinted for approximately six weeks, the splint was removed and was replaced by a 18F catheter Three days later this catheter was removed and the cystostomy tube was clamped The patient was able to void easily with perfect control He had some urgency and mild dysuria which subsided within 72 hours A catheter was then reinserted through the perineum into the bladder The cystostomy tube was removed and the abdomen healed By April 14 complete healing had occurred The patient was discharged from the hospital relatively free from urinary symptoms

It was necessary for the patient to report to the hospital at intervals of 2 weeks for dilation of the perineal urethrostomy due to stenosis at the skin margin He was dilated 3 times, the interval for dilation extended to 1 month and later to 3 months The patient now has a good urinary stream, nocturia 0–1 times and is pursuing his normal occupation The caliber of the urethra at the skin margin is maintained at 24F by dilation every 3 months There is no evidence of local recurrence of the tumor or of metastases

## SUMMARY

Successful construction of a perineal urethra with urethrostomy, by split thickness skin graft, following complete loss of the urethra distal to the triangular ligament has been presented

One case was a secondary procedure following traumatic avulsion of the penis Another was a primary procedure following total excision of the penis for carcinoma of the bulbous urethra

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# PARAURETHRAL CYST WITHIN THE CORPUS CAVERNOSUM URETHRAE

## CHARLES G WELLER

Cysts occurring within the urethra or arising from the prostate gland have been encountered on numerous occasions but, insofar as we have been able to ascertain, none has been previously observed within the corpus cavernosum urethrae

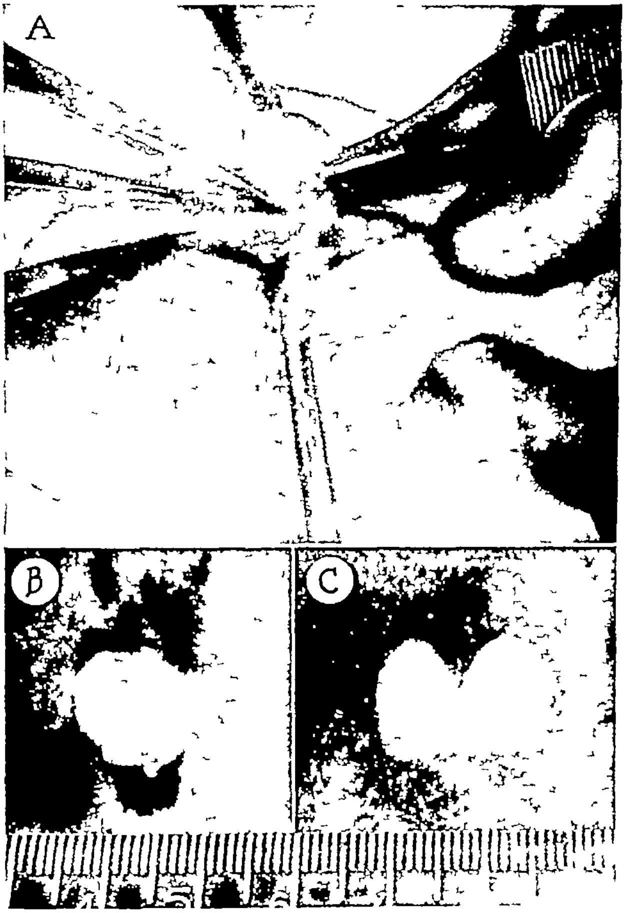

FIG 1 *A*, dissection of cyst from corpus cavernosum urethrae *B*, gross specimen unopened (external view) *C*, gross specimen bisected showing mucosal lining

The case which we wish to report concerns Mr S , a white man aged 33 years, who complained of a circumscribed, painless swelling on the ventral surface at the penoscrotal angle It measured approximately 1 5 by 1 0 cm , was tensely fluctuant and lay in the corpus spongiosum The patient had been aware of its

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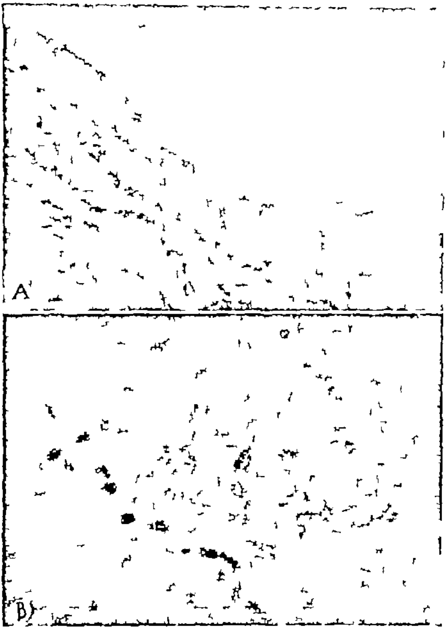

Fig 2 *A* mucosal lining ×430 *B* mucosal lining ×970

presence for only 2 weeks Urethroscopy showed compression of the urethra in the region of the mass There was no other intraurethral lesion

On June 2, 1955 the mass was exposed surgically and excised It consisted of a tense cyst lying in the ventral portion of the corpus spongiosum On removal no connection with the urethra was found There was a thin layer of cavernous tissue between the cyst and the urethral floor Microscopic study showed the cyst to be lined by transitional columnar epithelium and filled with thick slightly green to brown, purulent secretion (figs 1 and 2)

### DISCUSSION

A complete review of the medical literature pertaining to urethral cysts was made by Wesson[1] in 1925 Only sporadic case reports have appeared since that time He classifies urethral cysts as follows a) echinococcus cyst, b) cysts in connection with carcinoma of the prostate, c) Cowper's gland cysts, d) Littre's gland cysts, e) cystic adenoma, f) cystic dilatations of the utricle or ejaculatory ducts, g) retention cysts They may be congenital or acquired by either compression of ducts or vicarious development of mucus glands He states that

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[1] Wesson M B Cysts of prostate and urethra J Urol **13** 605-632 1925

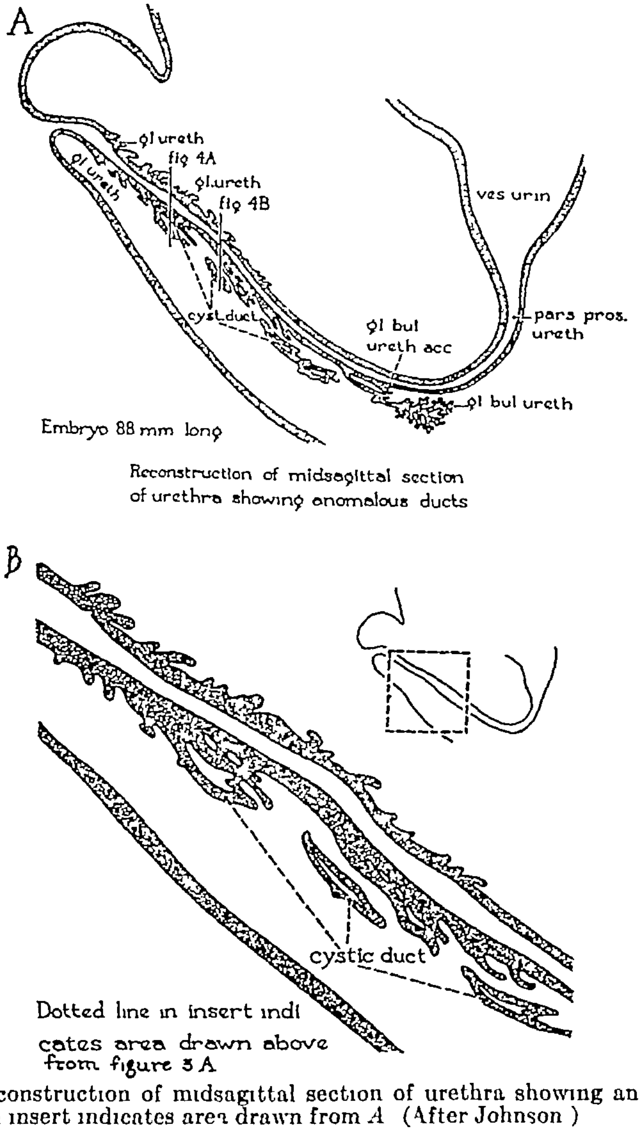
A
gl ureth fig 4A
gl.ureth fig 4B
gl ureth
ves urin
cyst. duct
gl bul ureth acc
pars pros. ureth
gl bul ureth
Embryo 88 mm long
Reconstruction of midsagittal section of urethra showing anomalous ducts
B
cystic duct
Dotted line in insert indicates area drawn above from figure 3 A

FIG 3 *A*, reconstruction of midsagittal section of urethra showing anomalous ducts *B*, dotted line in insert indicates area drawn from *A* (After Johnson )

"In the male it is generally considered that cysts of the anterior urethra arise from glands of Littre while those of the prostate, vesical orifice and posterior urethra originate in the prostatic tubules Grunfeld, Schwerin and Gottfried have reported small intra-urethral cysts of the glands of Littre Retention cysts due to occluded prostate gland ducts are the most interesting and the commonest " Wesson collected 55 cases from the literature, twenty-nine of which were prostatic in origin, and added four prostatic cysts of his own Among these cases, he found only four definite and three questionable reports of cysts of the anterior urethra All of these occurred within the urethral lumen

In a report on histologic studies of the urethra in the newborn, Montella[2]

[2] Montella, G Para-urethral glands and canaliculi in newborn infants Pediatria, 47 490-505 1939

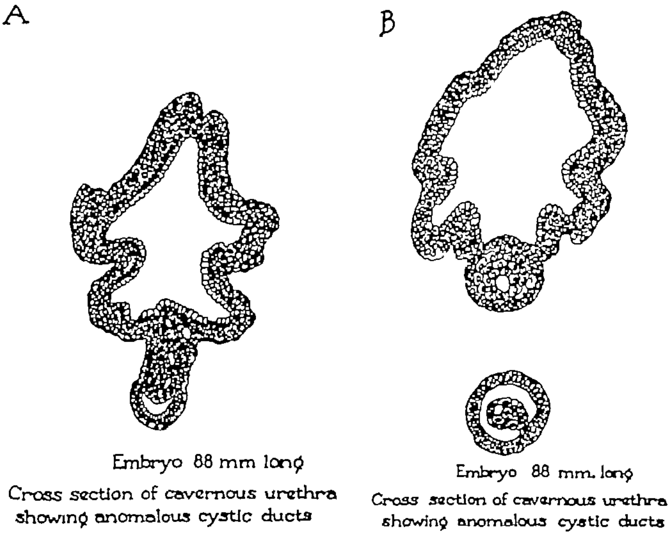
A
B
Embryo 88 mm long
Cross section of cavernous urethra showing anomalous cystic ducts
Embryo 88 mm. long
Cross section of cavernous urethra showing anomalous cystic ducts

FIG 4 *A* cross-section of cavernous urethra showing anomalous cystic ducts *B* cross section of cavernous urethra showing anomalous cystic ducts (After Johnson )

describes submucosal and mucosal glands, very few of which occurred on the ventral portion of the urethra

Montpellier and Laffargue[3] suggest as the cause of periurethral and vaginal cysts 'the embryologic migration and separation of glands " Langer and Schiftan[4] believe that cysts in the mucosa are usually of inflammatory origin but rarely congenital

We are of the opinion that the lesion occasioning this paper could have been acquired through isolation of a urethral gland by destruction of its duct or it could have resulted from a congenital epithelial channel such as described by Franklin Johnson[5] in 1920 in his studies of the embryonic urethra In one specimen Johnson reported epithelial channels along the ventral surface in the median line completely isolated from the urethra and containing a lumen (figs 3 and 4) The following is a quotation from his article That these ducts are derivatives of the urethra cannot be questioned for their epithelium is similar to that of it At first glance they give the appearance of being cut off epithelial glands, but this view of their origin is untenable, not only because of their larger size but because in certain places glands are seen arising from them

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[3] Montpellier J and Laffargue Pathogenesis of peri urethral cysts Bruxelles Med **13** 515-525 1933

[4] Langer E and Schiftan W Cysts and varices of anterior urethra in young men Dermat Wchnschr **91** 1562-64 1930

[5] Johnson F P Later development of the urethra in the male J Urol **4** 447 1920

"Why the formation of these peculiar structures and what their ultimate fate may be I am unable to state since in no other embryo have I seen anything comparable to them Nor have I been able to find any reference to similar structures in the literature It is difficult to conceive that the ducts which I have just described are para-urethral ducts in the making, for they show no external opening and are far more extensive than the usually described para-urethral ducts "

In the case we are reporting, the type of lining and absence of communication with the urethra argue for the congenital origin of this lesion

## SUMMARY

A case of paraurethral cyst, probably of congenital origin, in the ventral portion of the corpus cavernosum urethrae is reported

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# CYTOCHEMICAL OBSERVATIONS ON THE CORPORA AMYLACEA OF THE HUMAN PROSTATE GLAND

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The corpora amylacea found in the glandular acini of the prostate have been since the time of the earliest gross and microscopic studies of the prostate gland, a subject of much curiosity, investigation and subsequent confusion. Due to the fact that corpora are found within a glandular acinus, the greater part of the literature on the corpora amylacea is interwoven with that of the prostatic acinar secretion.

It is believed that a number of recently developed and perfected cytochemical methods make it possible not only to further localize and characterize but also to postulate perhaps on the physiological and possibly the clinical significance of the various proteins, carbohydrates, and lipids contained within these corpora. Consequently, this investigation concerns itself with the cytochemical localization, identification, and possible metabolic significance of the histochemical demonstrable lipid, carbohydrate, and polysaccharide components of the corpora in both normal and pathological human prostate gland.

## MATERIALS AND METHODS

Specimens obtained from 15 cases of benign hyperplasia of the prostate, ranging in age from 46–73, were studied.† Both normal and pathological tissue specimens were secured from the same prostate for comparative study.

Lipids were studied in freshly frozen sections (10–15$\mu$), gelatin imbedded blocks fixed in 10 per cent neutral formalin, neutral buffered formaldehyde (Lillie '47), formal-calcium (Baker '48), formal-calcium cobalt (Baker '46), and weak Bouin's fluid (Baker '46). The total lipid and neutral fat content was visualized by the following staining procedures: Sudan Black B, Sudan III (Herxheimer's '04 mixture), Oil Red O, and Oil Blue N, and Nile Blue Sulphate (Lison '36 and Cain '47), for the demonstration and identification of the phospholipids, the acid haematin method of Baker ('46) followed by the pyridine extraction procedure was used. The presence of metachromatic phosphatides was established by the use of Feyrter's ('36) tartaric acid thionin mixture.

For the study of cholesterol and its esters, the Lieberman Burchardt reaction, Schultz method (Romieu '27 modification) and the digitonin reaction (Lison '36) with subsequent staining by Sudan III were employed. Unstained frozen sections cut at 10–15$\mu$ were observed both in a dark field and in polarized light for birefringence.

The total reactive polysaccharide content, including the protein and lipid

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* My cordial thanks for the valuable technical aid of Miss Sheila Stahl.

† These specimens were obtained through the courtesy of the Department of Urology, Long Island College Hospital, Brooklyn, N. Y.

bound moieties such as glycogen, glycoprotein, and glycolipids was determined by staining in the periodic acid leucofuchsin technique (McManus '46, Hotchkiss '48, Lillie '47, '50) Glycogen was further separated and identified by the use of salivary digested control slides followed by the PAS and Bauer-Feulgen methods In addition, the dialyzed iron method of Hale ('46) and Rinehart and Abul-Haz ('51) was also used for demonstration of acid mucopolysaccharide Control sections were extracted with bovine hyaluronidase for varying periods up to 24 hours at 37°C at a concentration of 1 mg /cm $^3$ of phosphate buffer at pH 7 0

Observations on the nucleoproteins and their characteristic basophilia were carried out on sections fixed in Carnoy's fluid, 10 per cent neutral formalin, absolute alcohol, and Zenker-formal Desoxyribonucleic acid (DNA) was investigated by means of the Feulgen-Schiff reaction, and the methyl-green pyronin methods of Brachet ('42), Kurnick ('52) To further verify the specificity of the nucleic acids the following procedures were used 1) incubation of sections with crystalline desoxyribonuclease in a concentration of 0 1 mg /ml solution in McIlvaine's buffer, pH 6 5 at room temperature for intervals of 1, 2, and 6 hours to selectively remove DNA, and 2) incubation of sections for 1 hour at 45°C with crystalline ribonuclease at a concentration of 0 01 mg /ml solution in McIlvaine's buffer at pH 6 5 to selectively remove DNA

The occurrence and distribution of the basophilia characteristic of the nucleoproteins was further studied by staining with Mallory ('38) eosin-methylene blue, and a 5 per cent toluidine blue solution Two control sets consisting of two slides each were utilized for the determination of the effects of ribonuclease and desoxyribonuclease These slides were incubated for varying periods up to 24 hours in the following solutions 1) crystalline ribonuclease in a concentration of 01 mg /ml or a 1 per cent solution in McIlvaine's citric acid disodium phosphate buffer at pH 6 5 at 45°C, and 2) desoxyribonuclease in a concentration of 0 2 mg /ml of McIlvaine's buffer at pH 6 5 at room temperature These two control sets together with an untreated control set were stained simultaneously in either eosin-methylene blue or toluidine blue

## LIPIDS

The lipid content of the normal and pathological human prostate with its secretions and associated corpora amylacea has been a subject of much investigation and subsequent confusion by workers throughout the years It has been assumed by many workers that the corpora are composed of a substratum of lipid substance, because of the known presence of phospholipids in the prostatic secretion Furbinger ('11) concluded that the corpora were composed of lecithin, while Bjorling ('12) and Posner ('11) suggested that the lecithin united with a protein from degenerating cells to form a lecithalbumin

A cursory survey of gelatin-imbedded frozen sections of both normal and hyperplastic prostatic tissue, stained with oil-soluble dyes, Sudan III (Herxheimer's '04 mixture) Oil Red O, and Nile Blue N, and Sudan Black B, showed three distinct distributions of the neutral fat and phospholipids within the corpora amylacea, namely, 1) small, but discrete droplets of neutral fat similar

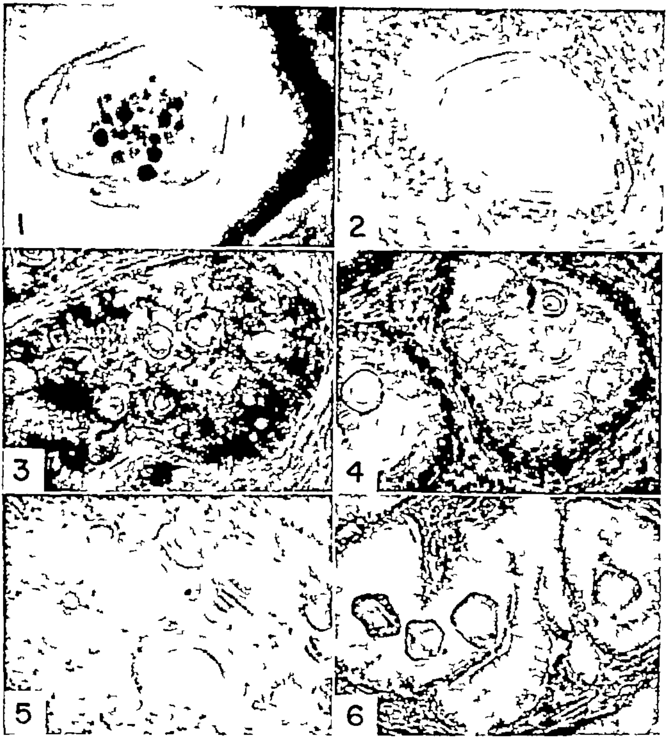

FIG 1 Localization of neutral fat and phospholipids in a corpora amylacea Fixation 10 per cent neutral formalin frozen section Sudan Black B ×200

*2* Distal cytoplasm of a prostatic acinus contains very fine sudanophilic bodies These cells are actively discharging Corpora amylacea display no sudanophilia Fixation 10 per cent neutral formalin frozen section Sudan Black B ×200

*3* Localization of phospholipids in prostatic secretion Note that corpora amylacea are negative Fixation Formaldehyde-calcium frozen sections Baker's acid haematein test ×200

*4* This preparation was subjected to Baker's control procedure extraction with pyridine Positive staining thus confirming presence of phospholipids Fixation Formaldehyde calcium frozen sections Baker's 46 acid haematein test with pyridine extraction ×200

*5* Corpora amylacea contain RNA (red) Note that corpora here are lying in connective tissue epithelium of acinus has degenerated Fixation Carnoy Methyl green pyronin Kurnick (52) ×200

*6* Localization of acid mucopolysaccharides in corpora amylacea Fixation 4 per cent neutral formalin Dialyzed iron method of Rinehart and Abul Haz (51)

to that stained with Sudan Black B (fig 1), in the center of the corpora, 2) the most peripheral layer and an intermediate layer exhibit a weakly positive but diffuse reaction with the oil soluble dyes in those corpora which are laminated (fig 1 *2* and *3*) a diffuse but weak positive sudanophilia throughout the corpora

The periphery of the outermost lamina may exhibit a weak diffuse sudanophilia due to a surface condensation phenomenon

In addition, the corpora display no sudanophilia, although the distal cytoplasm of the acinar cells displays very fine sudanophilic (Sudan Black B) inclusion bodies (fig 1, *2*) Comparison with slides prepared and stained with anilin acid fuchsin methyl green method of Bensley reveals that the fine inclusion bodies in the distal cytoplasm are probably mitochondria

The last two described localizations of sudanophilia occur with the greatest frequency in both normal and hyperplastic prostatic tissue Only rarely is a corpus seen to contain a nidus of fat droplets, although free droplets of neutral fat are frequently encountered in the flocculent prostatic secretion, as had been noted by earlier investigators (Posner and Rapoport '05, Fischel and Kreibich '11, Kinoshita '20, and others) My observations do not confirm the belief of the older workers that the corpora were invariably built about the droplets of neutral fat contained in the prostatic secretion

The Sudan Black B technique of Baker ('46) is most valuable in the identification of lipids when used in conjunction with procedures such as the acid-haematin procedure of Baker ('46), followed by his pyridine extraction technique in order to distinguish between the phosphilipids and other non-lipid material With the Baker's acid haematin method, the corpora remained unstained (fig 1, *3*) while the flocculent prostatic secretion showed a positive blue-black reaction With the Baker's pyridine control (fig 1, *4*), both the prostatic corpora and secretion remain negative

It is generally conceded that the Baker's acid haematein test and the control pyridine extraction is specific for the histochemical demonstration of the ester phosphatides which includes the phospholipids (Pearse '51) Therefore, one can conclude that the phospholipids, namely lecithin, cephalin, and sphingomyelin form a large part of the lipids found in the prostatic secretion in both normal and hyperplastic human prostates, while the corpora amalycea remain negative This histochemical finding is in agreement with the chemical evidence supplied by such workers as Huggins and Johnson ('33), Moore and Hanzel ('36), Scott ('45), Lundquist ('46), and others In the present state of histochemistry, absolute identification and separation of the various ester phosphatides cannot be made Further corollary evidence on the presence of lecithin in the prostatic secretion and corpora was obtained by the use of a 1 per cent Nile Blue sulphate solution (Lison '36), and the Nile Blue method of Cain ('47) A strong positive blue color was found by both the aforenamed procedures in both the prostatic secretion and corpora It was found by Cain ('47) that only lecithin and oleic acid would stain blue appreciably with 1 per cent Nile Blue sulphate In general, the corpora stain different shades of blue with the darker parts in the center (Moore and Hanzel, '36) There are occasionally concentric layers of the corpora which stain light orange or red, and infrequently the center of the corpora may show small orange, or rose colored droplets These droplets are probably the neutral fat droplets already described

Further confirmatory evidence on the presence of the ester phosphatides was supplied by the use of the tartaric thionin mixture of Feyrter ('36) which revealed a definite metachromasia only in the outer lamina of the laminated corpora amylacea. There is no doubt according to Pearse ('51) that the phosphatides are the principal lipid substances demonstrated by Feyrter's method, and this is presumably an account of the contained phosphoryl group which induces this metachromasia.

Using the same method, Feyrter ('36, '42), and Pretl ('48) describe the metachromatic reaction of lipoids and lipo protein complexes in the human prostate. However, interference due to the presence of acid mucopolysaccharides (fig. 1, *6*) makes it difficult to ascertain small quantities of combined lipids such as lecitho protein or other protein phosphatide complexes. In addition, the metachromasia may have been enhanced by the acidic nature of the phospholipids as revealed by the use of Cain's ('47) method employing Nile Blue sulfate.

## BIREFRINGENCY

Examination of unstained sections in both a dark field and with polarized light revealed when present a plain birefringence in both the corpora and prostatic secretion. Most corpora amylacea exhibited no birefringency whatsoever. When present the anistropic material of the corpora was 1) either in the form of fine particles in the outer lamina, or 2) as foci located in the center of a corpus. No Maltese cross-birefringency was observed, although a double refraction of the whole corpus was reported by Posner and Rapoport ('05), Posner ('11), Moore and Hanzel ('36). The birefringency of the prostatic secretion at best was "spotty."

The localization of the birefringent lipids in the corpora and prostatic secretion can be most readily correlated with the distribution of neutral fat, although Moore and Hanzel ('36) ascribe the double refraction of the corpus due to the presence of crystalline purines which are derived from the nucleoproteins.

Since the distribution of neutral fat is extremely variable and tends to be "patchy" in both corpora and prostatic secretion the birefringent lipids likewise are extremely variable in localization, and furthermore are not constant even within the same prostate or age group. Evidently, the neutral fat is in such a crystalline state that it exhibits only a plain birefringence (Lison '36, Pearse '53). The failure, however, to form spherocrystals and the resulting Maltese cross-type of birefringence does not exclude the presence of cholesterol and its ester. Kinoshita ('20) reported the Maltese cross type of birefringency which is characteristic of cholesterol and its esters in both the prostatic epithelium and secretion in man.

The presence of cholesterol and its esters was revealed by a strong positive, but diffuse blue-green reaction in the flocculent prostatic secretion and rather infrequently in the corpora when the Liebermann Burchardt reaction and the Schultz method (Romieu '27 modification) was used. Kinoshita ('20) reports free cholesterol to be of frequent normal occurrence in man. Further confirmatory evidence on the presence of cholesterol was obtained by using a 0.5 per cent alcoholic solution of digitonin, the digitonin-cholesterol complex in both the corpora and prostatic secretion became evident Subsequent staining of the digitonin-treated sections with Sudan III revealed that the cholesterol esters became colored and lost their birefringence, when present, while the crystals of cholesterol-digitonin complex remained anisotropic and colorless

### CARBOHYDRATES

The total reactive polysaccharide content of corpora, including the protein and lipid-bound complexes such as glycogen, glycoprotein, and glycolipids was visualized by staining with the periodic-acid leucofuchsin technique (Hotchkiss '48, McManus '46, Lillie '47, '50) Application of the PAS technique reveals a moderately positive reaction in both the corpora and the flocculent prostatic secretion Control sections extracted with hyaluronidase for varying periods up to 24 hours at 37°C at a concentration of 1 mg /cm $^3$ of phosphate buffer at pH 7 0, and then stained with PAS technique showed some loss of stainable reactive material in both corpora and the prostatic secretion Saliva digested slides revealed no diminution in the PAS reactive material in the cells

In other sites, the PAS positive material was confined to the basement membranes underlying the epithelium, around small blood vessels, and enclosing smooth muscle cells

There is some interference in PAS reaction due to the presence of lipids, and the glyco-lipid complexes With the performic acid-Schiff method (Pearse '51, Lillie '52) a strong positive reaction in flocculent prostatic secretion was obtained which can be interpreted as indicating the presence of either phospholipids or cerebrosides with unsaturated bonds

The identification and localization of the acid mucopolysaccharides present in the corpora amylacea were obtained by use of the dialysed iron method of Hale ('46) and its modification by Rinehart and Abul-Haj ('51) By these methods, the acid mucopolysaccharides were localized in the corpora (fig 1, *6*) Treatment with hyaluronidase did not diminish the blue staining of the mucopolysaccharides

### NUCLEOPROTEINS

It has been assumed rather logically by many investigators that proteins, particularly nucleoproteins, are an important component of those bodies since the corpora contain desquamated acinar epithelial cells and are formed from the prostatic fluid Indirect chemical evidence that nucleoproteins form an important constitutent of the prostatic corpora amylacea was presented by Moore and Hanzel ('36) They also suggested that the secondary softening of the corpora was brought about by the nuclease group of enzymes, and that double refraction of corpora is due to the crystalline purine bases of the nucleoproteins

In both normal and hyperplastic human prostates, a marked positive homogeneous (red) reaction, indicating the presence of RNA could be detected in the corpora amalycea (fig 5) by the Feulgen-Schiff method, and the methyl-green pyronin method of Brachet ('42), Kurnick ('52) Incubation with crystalline ribonuclease for 1 hour at 45°C at a concentration of 0 01 mg /ml solution in

McIlvaine's buffer at pH 6 5 did not selectively diminish or remove the DNA in the corpora

The desoxypentosenucleic acid (DNA) as visualized by the Feulgen-Schiff reaction demonstrated clearly the nuclear chromatin of the desquamated acinar epithelial cells incorporated in corpora or free in the prostatic secretion Incubation with crystalline desoxyribonuclease in a concentration of 0 1 mg/ml solution in McIlvaine's buffer, pH 6 5 at room temperature for intervals of 1 2, and 6 hours removed progressively with increased extraction times larger amount of DNA A condensation of both DNA or RNA was observed along the boundaries of some of the concentric lamina of the corpora

The associated basophilia of the nucleoproteins investigated by means of Mallory's ('38) eosin methylene blue method, and with staining by 0 5 toluidine blue, clearly showed the cellular chromatin material either incorporated in the corpora or free in the prostatic secretion With toluidine blue staining there was a faint residual basophilia of both the homogeneous and laminated corpora, which was resistant to extraction with both ribonuclease and desoxyribonuclease The nuclear basophilia was unaffected by treatment with ribonuclease, but was progressively diminished by treatment with desoxyribonuclease The acidophilia of the corpora with Mallory's eosin methylene blue was unaltered by treatment with the above named enzymes Furthermore, no secondary softening of the corpora occurred with either ribonuclease or desoxyribonuclease for incubation periods as long as 24 hours, although Moore and Hanzel ('36) state that secondary softening of the corpora is brought about by the *in vivo* nuclease enzymes present in an actively secreting prostate

On the basis of the afore described histochemical observations, it is valid to say that the nucleoproteins are a constituent of the prostatic corpora amylacea It may be true, however, as Moore and Hanzel ('36) suggested that the nucleoproteins are broken down in the corpora, and that the present histochemical tests are not sensitive enough to detect their degeneration products Ultraviolet ray absorption analysis of the nucleoproteins in the corpora amylacea are in progress and these studies will be reported on later

## SUMMARY

Histochemically, no significant changes occur with age in the normal or pathological human prostate as to the lipid, carbohydrate and nucleoprotein content of corpora amalycea Thus the corpora amylacea cannot be used as a diagnostic tool to ascertain the physiological state of the prostate It can be said however, that with increasing age the number and size of the corpora generally increase and that the number of corpora and the amount of sudanophilic lipids contained in the prostatic acinar epithelium, the acinar lumen and the supporting connective tissue stroma increases with age but not invariably so

The lipids contained in the corpora amalycea are neutral fat cholesterol, and phospholipids probably lecithin There is evidence to indicate that the lipids form lecithoprotein, and protein phosphatide, glyco-lipid complexes

Both ribonucleic and desoxypentose nucleic acid form an important constituent of the prostatic corpora amalycea

The total-reactive polysaccharide content of the corpora includes glycogen as well as the protein and lipid-bound complexes such as the glycoproteins, and glycolipids

The author wishes to express her thanks to Mr Steve Montes for his aid in preparing the photographs

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# PROSTATIC CORPORA AMYLACEA

GEORGE C PRATHER AND DAVID SKINNER

*From the Urological and Pathological Services of the Newton Wellesley Hospital Newton Mass*

The purpose of this paper is to describe the urethral manifestations of a condition frequently seen by cystourethroscopic inspection of the prostatic urethra but which is not described in any of the current urological texts that I have consulted Although the condition may not be of serious import, it has been the only objective finding in some patients with urgency and microscopic hematuria A similar cystoscopic picture is not infrequently seen in the region of the bladder neck in women

Cystoscopic inspection of the prostatic urethra or examination of a gross specimen of prostate gland sometimes shows scattered, minute, black specks in or beneath the mucous membrane of the prostatic urethra In color and size they resemble particles of coal dust, or black pepper (fig 1) These black specks do not rub off the epithelial surface nor can they be removed by irrigation They should not be confused with larger, black, pinhead sized stones occasionally seen protruding from prostatic ducts, as described by Huggins and Bear

Similar minute dark brown or black particles throughout the substance of the prostate have also been noted and studied over a long period of time, and we believe the composition of the concretions throughout the gland is identical with those concretions that we hereby describe in the epithelium of the prostatic urethra

The condition has been described numerous times under the titles of prostatic concretions, corpora colloidea, corpora amylacea, amyloid bodies, and corpora hassalliana, and is to be differentiated from the true prostatic calculi that contain inorganic salts

An historical review of studies made on prostatic concretions' reveals the remarkable powers of observation and detailed findings of those who have been interested in the subject The first recorded remarks on this subject that I have been able to find were described by Morgagni in 1779 who stated, "That is to say, in the prostate gland, which was enlarg'd, and in its external circumference, of a red color inclining to brown I found within the remaining part of its substance which was in other respects in a natural state, granules of tobacco as it were of a yellowish colour inclining to blackness and those in several places

"These appearances were not far from the internal surface of the urethra, some lying scattered up and down at a considerable distance from each other, and some being crowded together into one cavity, much less than that whereof I just now spoke

' But of what nature are these granules? For I have found them in many bodies, and not then for the first time In the Adversaria (r), I considered them as a humour which is secreted in the prostate, and coagulated into that form nor do I

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Read at annual meeting South Central Section of American Urological Association San Antonio Texas October 17-19 1955

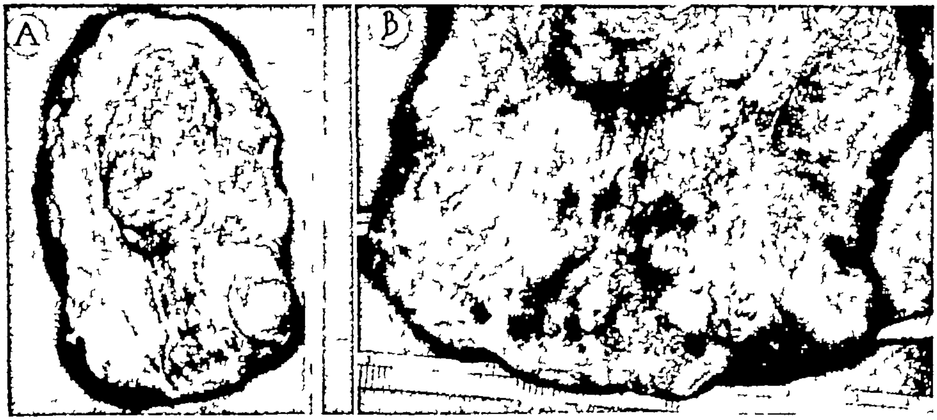

FIG 1 *A*, hypertrophied bladder with enlarged prostate and black speckling of urethra *B*, close view of prostatic urethra shows coal-dust-like deposit, particularly in region of verumontanum

at present see any reason why I should not consider them in the same point of view also "

Now, 176 years later, there appears to be no reason to urge Morgagni to reconsider his report, even if we could

Although Home (1811) recognized the frequent presence of phosphatic, oxalate and uric acid stones in the bladders of patients with prostatic obstruction he did not mention any substances in the prostate itself that could be called "concretions " John Adams (1853) however described ' prostatic concretions" in detail as Jones (1847) had done a few years previously Concretions of microscopic size located in the follicles of the prostate gland were linked potentially to calculi in the prostate

Wedl (1855) gave the subject thorough study and was aware of the presence of concretions in the "central extremities of the excretory ducts toward the urethra" as well as in the parenchyma of the prostate After chemical tests, Wedl concluded that these concretions were composed principally of an organic substance and that they should be termed "colloid corpuscles," and stated that the name of "corpuscula amylacea" had been used by Kolliker and Virchow

Sir Henry Thompson (1873) presented a splendid account of the substances which we are describing in this paper His description merits the following quotation "It is exceedingly common, when a urethra has been laid open, to observe in its prostatic part, lying around the verumontanum, and in the orifices of the prostatic ducts especially, numerous little brownish or blackish bodies, the largest of which ordinarily met with are about the size of poppy seeds They do not lie free in the canal, but generally just within some of the orifices alluded to, sometimes beneath the epithelial layer of the mucous membrane of the urethra, barely visible over them Again when a section of the prostatic substance is made, especially if a knife be directed backwards and outwards on either side of the verumontanum, many of the same bodies may be frequently seen These bodies have received the name of prostatic concretions They have in their origin, no relation to urinary calculi "

Thompson found the concretions to be from $\frac{1}{1000}$ to $\frac{1}{100}$ of an inch in diameter and they were not generally observed before middle or advanced age With the aid of chemical examinations by Dr William Squire, Thompson concluded that the "organic constituent of the concretions is not a true protein body, but most probably belongs to that class of nitrogenous substances, sometimes termed protein derivatives, of which fibroin, gelatin, and chitin are examples " Thompson concluded that their existence was a necessary result of the performance of natural functions on the part of the prostate and that they were the result of pathological exudation frequently occurring in various organs in advanced age

Eastman reviewed the subject in 1897 under the heading of "corpora amylacea" in the prostate, and mentioned that Virchow had described similar objects in the brain, spinal cord, at the neck of the bladder and in the so-called female prostate Eastman examined the prostate of 24 patients of all ages and after microscopic study reported that the bodies were situated in gland alveolae and ducts The smallest were not larger than an epithelial cell, the largest the size of a millet seed An epithelial origin was suggested because commonly the epithelium had split off from its wall forming an acinus, the cavity of which was filled with disintegrated epithelium He was of the opinion that concretions with broad concentric laminations were formed by direct metamorphosis of gland epithelium and that the metamorphosis had the character of amyloid degeneration

Moore published a very comprehensive study in 1936 under the title "Prostatic Corpora Amylacea and Calculi " *He feels certain that concrements designated* as corpora amylacea and clinically manifested prostatic calculi are directly related and have the same genesis The basic composition and the architecture of the matrix of the corpora amylacea and calculi were the same, the only essential difference being in the size and the infiltration of calcium salts

Moore believes that there is morphologic evidence to show that prostatic acini are filled with an albuminous fluid, in which there are suspended desquamated epithelial cells in all stages of degeneration, secretion granules droplets of anisotropic and isotropic lipid and the end products of cellular degeneration He speculated that the reason for the change of cells into gel like corpora might be explained on the basis of release of nucleic acid by cellular degeneration

Moore observed a gradual transition from tall columnar epithelium in the prostate to cuboidal epithelium in men over 50 years of age and suggested altered endocrine relations as a possible cause for the changing epithelial pattern He inferred that the cuboidal type of epithelium is more readily desquamated than the tall columnar type Increased fibrosis of the stroma of the prostate and a decrease of smooth muscle tissue may also contribute to cause partial obstruction of the ducts and consequent stagnation of secretion Furthermore, thrombosis in the prostatic plexus could result in passive hyperemia of the prostate and, as in any glandular organ, cause increased desquamation Infection is believed to have no direct relation

Moore studied concretions with polarized light and crossed Nicol prisms as well as the effect of organic solvents and alkalies on the concretions The effect of the substances in the concretions on polarized light was believed due to the presence of one or more crystalline purines (adenine xanthine and hypoxan

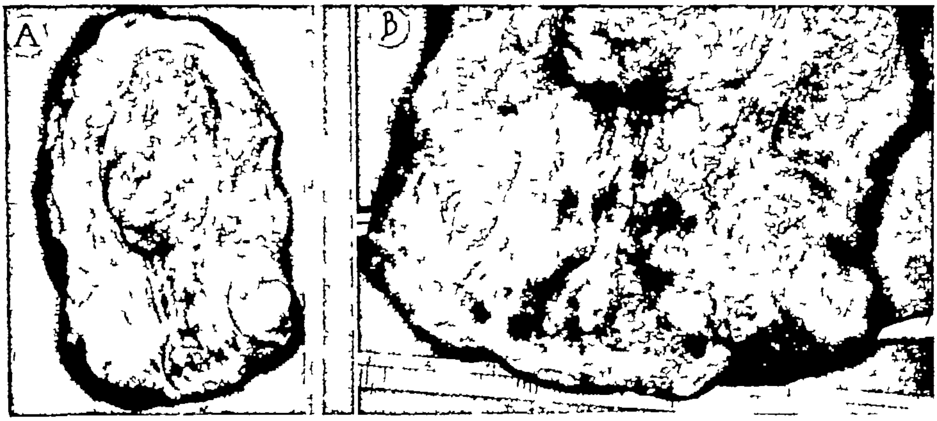

FIG 1 *A*, hypertrophied bladder with enlarged prostate and black speckling of urethra *B*, close view of prostatic urethra shows coal dust like deposit, particularly in region of verumontanum

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## ABSTRACTS OF CASES

A brief description of a few case histories with attached histological findings follows

*Case 1* A man 71 years of age entered hospital with severe cardiac failure and died shortly thereafter Autopsy demonstrated the gross findings (fig 1) A microscopic section of one of the blackish deposits is shown in figure 2

*Case 2* A man 67 years of age entered hospital with a history of frequency and dysuria of 10 days' duration Rectal examination demonstrated a small prostate of normal consistency The urine sediment showed 1 to 15 red blood cells Cystoscopy found prominent lateral lobes with numerous small black deposits in the region of the prostatic ducts There was no residual urine in the bladder following voiding Roentgenogram showed no opacities in the region of the prostate Pyelograms were normal

Cystoscopic biopsy of the coal-dust like deposits was performed (fig 3) Symptoms were relieved following bladder irrigation and hot sitz baths

*Case 3* A man 56 years of age entered hospital for gallbladder surgery and died from cardiac arrest on the operating table No urinary symptoms were recorded in his history, and the size of his prostate was not reported in the record of his physical examination

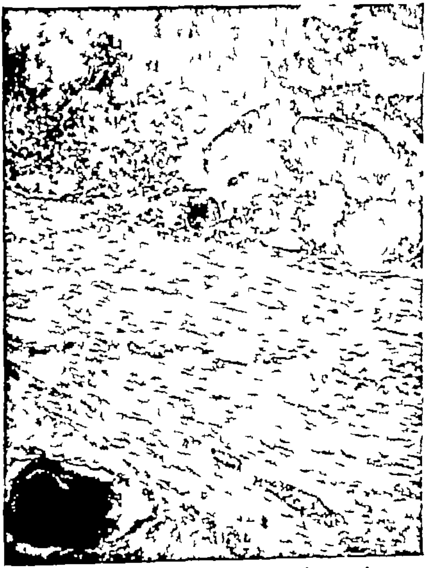

FIG 2 Microscopic section of prostatic urethra shows plaques in intraepithelial spaces of periurethral gland at the top Intervening fibrous tissue in central portion and a similar aggregate in a prostatic duct in the lower left hand corner

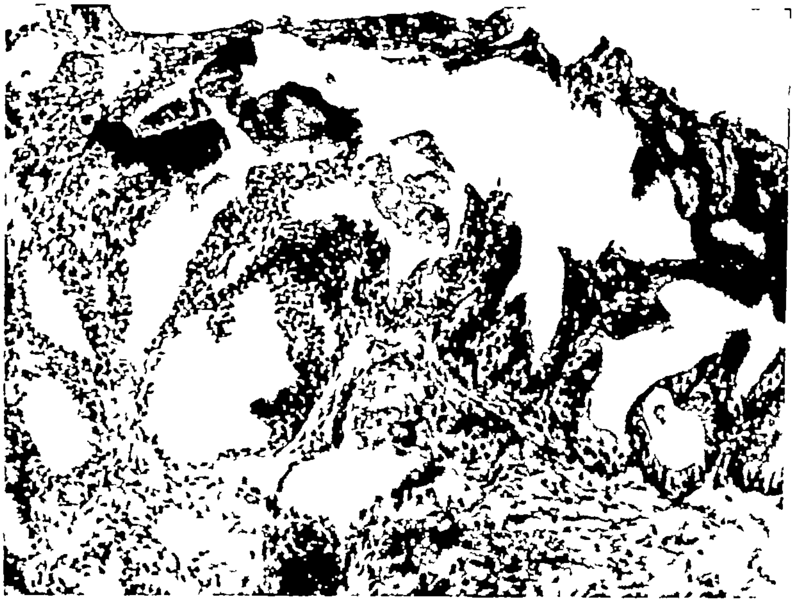

FIG 3 Microscopic section of urethral biopsy shows superficial periurethral glands containing plaques together with amorphous debris, desquamated epithelial cells, and a few neutrophils

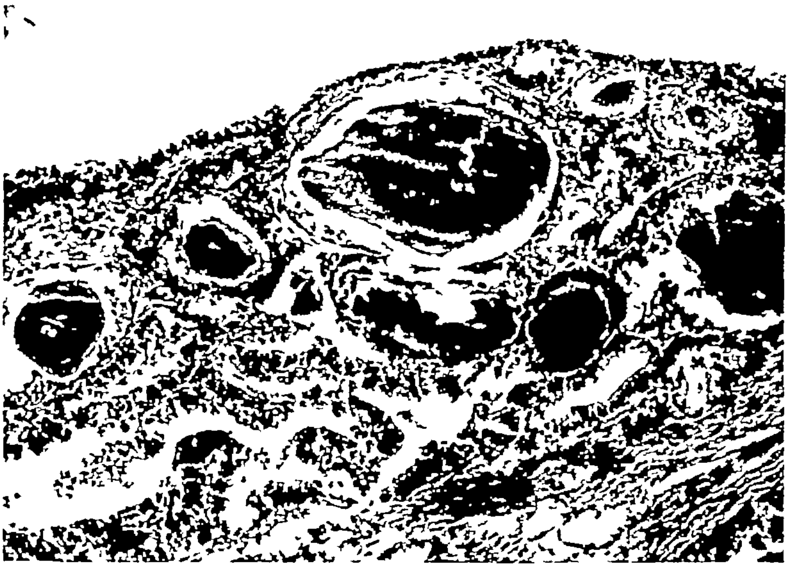

FIG 4 Microscopic section of verumontanum shows urethral surface at top with the underlying prostatic and periurethral ducts filled with plaques

An autopsy was done The prostate weighed 35 gm and was soft, rubbery and uniform In the prostatic urethra near the verumontanum there were numerous black flecks Sections of the prostate showed many glands containing corpora amylacea Sections of the verumontanum showed many of the ductular and gland-like spaces distended with red-brown aggregates, some of which were laminated and others which were irregularly dense (fig 4)

*Case 4* A man 65 years of age entered hospital because of gross hematuria On rectal examination the prostate was slightly enlarged firm and smooth

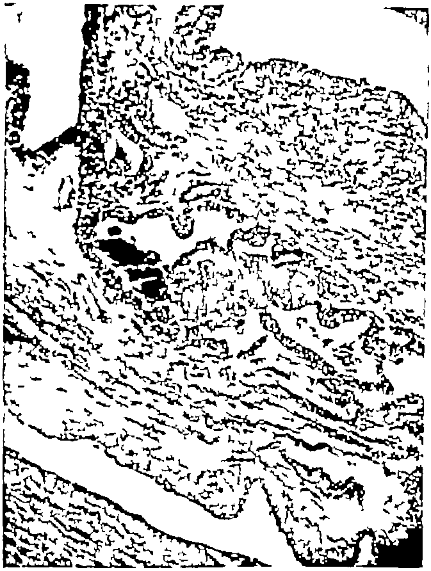

FIG 5 Microscopic section from prostatic urethra shows urethral surface at top deposits in a prostatic duct or gland and a lymphatic space at the bottom

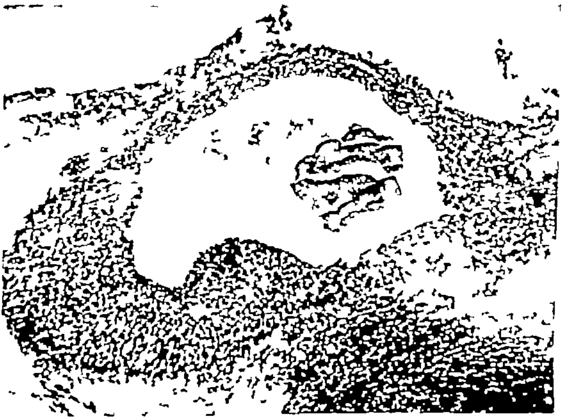

FIG 6 Microscopic section of the bladder shows surface epithelium at top with an underlying epithelial lined space containing a fragmented yellow brown plaque adjacent to amorphous debris admixed with inflammatory and epithelial cells

Urological study demonstrated a bladder tumor (papillary epithelioma, grade 2) and an obstructing prostate The bladder tumor was treated by electrocoagulation via suprapubic cystotomy Two weeks later suprapubic prostatectomy was done

The prostate weighed 58 gm and showed black coal-dust-like deposit in the region of the prostatic ducts Microscopic sections from the region of this black deposit showed glands and ducts containing corpora amylacea (fig 5)

*Case 5* A woman 63 years of age entered hospital with dysuria of two years' duration The urine showed a few red blood cells Intravenous urograms were normal Cystoscopy demonstrated several small, black, coal-dust-like deposits on the left side of the bladder neck Cystoscopic biopsy was done and the area treated by electrocoagulation Microscopic sections from the biopsy showed islets of cystic spaces lined with transitional cells containing brownish material (fig 6) Symptoms were relieved after these cystoscopic procedures

## SUMMARY

Description has been presented of coal-dust or black pepper-like spots in the mucous membrane of the prostatic urethra of the male and bladder neck of the female These small bodies are known in the literature as corpora amylacea or concretions, and are identical to similar bodies that may occur throughout the substance of the prostate On microscopic examination they consist of periurethral glands or ducts containing plaques, together with amorphous debris and desquamated epithelial cells

Studies by others, and those which we have had done, indicate a nucleoprotein as the substance inside the duct or gland The nature of the pigment remains obscure The suburethral concretions may occur in patients as an incidental finding but we have noted their presence in patients with urinary frequency, urgency, and slight microscopic hematuria and in whom no other abnormality could be found to explain the symptoms No specific treatment is suggested, although urethral dilatation and irrigation have been helpful in improving symptoms Resection of the involved area in the female or prostatectomy in the male may be considered only if symptoms are severe

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# FACTORS THAT EXPEDITE TRANSURETHRAL PROSTATIC RESECTION

PHIL A BLEAKNEY AND JOHN P PACKARD

Since transurethral resection of the prostate is one of the most arduous surgical tasks that confronts the urological surgeon and since there has been a paucity of articles on this subject during the past few years, it seems timely to review various factors that play a part in the expeditious performance of this procedure The factors to be discussed will be limited to those that affect the use of the Stern McCarthy standard model electrotome

In selecting these various factors to bring to your attention, only those were chosen that we felt might be particularly useful to the operator in eliminating unnecessary delays and they were classified as follows

1) Physical factors
   Those that affect the efficient function of the physical equipment needed to perform prostatic resection
2) Factors of technique
   These were selected to assist the resectionist in expediting the adequate removal of prostatic tissue by making each movement as productive as possible, avoiding unnecessary delays and maintaining tissue orientation
3) Factors of judgment
   Include those factors that assist the operator in planning his approach to and in making decisions during the operative procedure

## OUTLINE OF PHYSICAL FACTORS

1) A dark operating room provides
   A Relatively better vision through the telescope
   B Better concentration by the operator
2) The irrigating system
   A An isotonic irrigating solution reduces the risk of hemolysis
   B An ample and reserve supply of irrigation solution three feet above patient
   C The rubber tubing should be 1) of large lumen with equally large connectors, 2) of sufficient rigidity to avoid kinking during anterior resection, 3) free of air leaks which blur vision and increase explosion hazard test, and 4) suspended with elastic separate from electric cords
3) The instruments
   A Have ample supply to replace faulty equipment during operation Don't take time out for repairs
   B *Use a standard one size* 'free wheeling' resectoscope that preserves sense of touch

Read at annual meeting South Central Section of American Urological Association San Antonio Texas October 17-19 1955

C The loop shaft must be perfectly straight and drop in sheath with no binding

D Keep electrical equipment free of corrosion, connections tight, spark gaps properly spaced and a spare battery box complete with cord, clip and new batteries in reserve

A few comments regarding some of the physical factors mentioned in the foregoing outline may prove to be helpful We have found cytal satisfactory as an irrigating solution in that it is easily prepared, affords clear vision, and seems to have some clot-inhibiting effect The use of two 5-gallon jars of irrigating solution connected in series assures the operator of an ample supply of the solution for even the most troublesome transurethral surgery and eliminates the loss of time consumed in refilling smaller containers as well as the possibility of introducing air into the irrigating system The safety and success of transurethral surgery should be safeguarded by having available a reserve supply of all equipment used to insure satisfactory completion of the operation in the event any part of the equipment fails to function

### OUTLINE OF FACTORS OF TECHNIQUE

1) In placing the patient on the table, the less the thighs are flexed the more accessible is the prostate for resection (fig 1)

2) Plan orderly and adequate removal of tissue and avoid jumping from one field of operation to another
   A The plan described by Nesbit is one of avascularization in which he begins anteriorly and resects first a layer of juxtacapsular prostatic tissue (fig 2)
   B The plan described by Barnes removes the lobes in layers, working up and then down on the lateral lobes (fig 3)
   C The plan we follow partially includes the avascularizing principle of Nesbit plus an effort to resect downward in layers as much as possible

3) Maximum amount of tissue per cut removed by
   A Increasing the excursion of the loop by moving the sheath outward while making the cut, thereby increasing the length of tissue excised (fig 4)
   B Keeping the loop extended as far as possible while moving the sheath without sacrificing orientation (fig 5)
   C Using the triangular ligament as a fulcrum, the loop is pressed into the tissue by swinging the ocular end of the instrument away from the plane of the tissue being excised (figs 4 and 5)
   D Co-ordinating the aforementioned movements and completing the cut with the control handle, all the while trying to visualize the loop describing an arc similar to the contour of the prostatic capsule A sort of bowing motion as the maneuver is executed (fig 4)
   E Using the cutting current alone without blending it with coagulation

4) Removal of resected tissue from the bladder by
   A Using two evacuators alternately when tissue is impeding operation

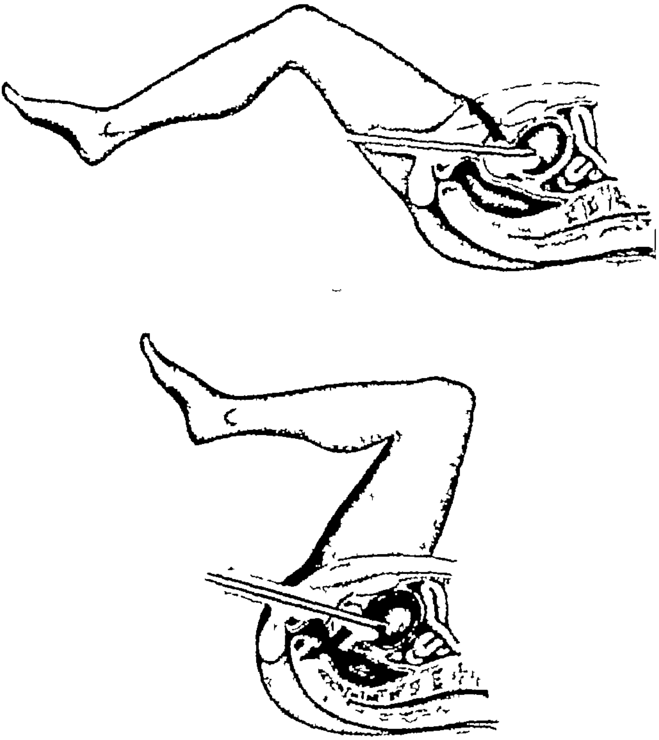

Fig 1 Upper drawing depicts proper position of thighs for prostatic resection Prostate is displaced upward into bladder and toward urethra Lower drawing shows improper position of patient Thighs are flexed too much throwing prostate outward toward perineum as for perineal prostatectomy (Courtesy of Barnes R W Endoscopic Prostatic Surgery St Louis The C V Mosby Co 1943 p 108 )

B Maneuvering intravesical end of sheath at each emptying of the bladder to allow irrigating solution to expel fragments Expulsive force of bladder preserved by low spinal

5) Small bits of tissue and clots adhering to loop many times can be removed by taking another cut

6) A strip of prostatic tissue not completely severed when loop has entered sheath may be sectioned by pushing entire instrument forward a short distance

In addition to the various factors of technique mentioned above there is one which may be called freedom of movement of the instrument, that is essential

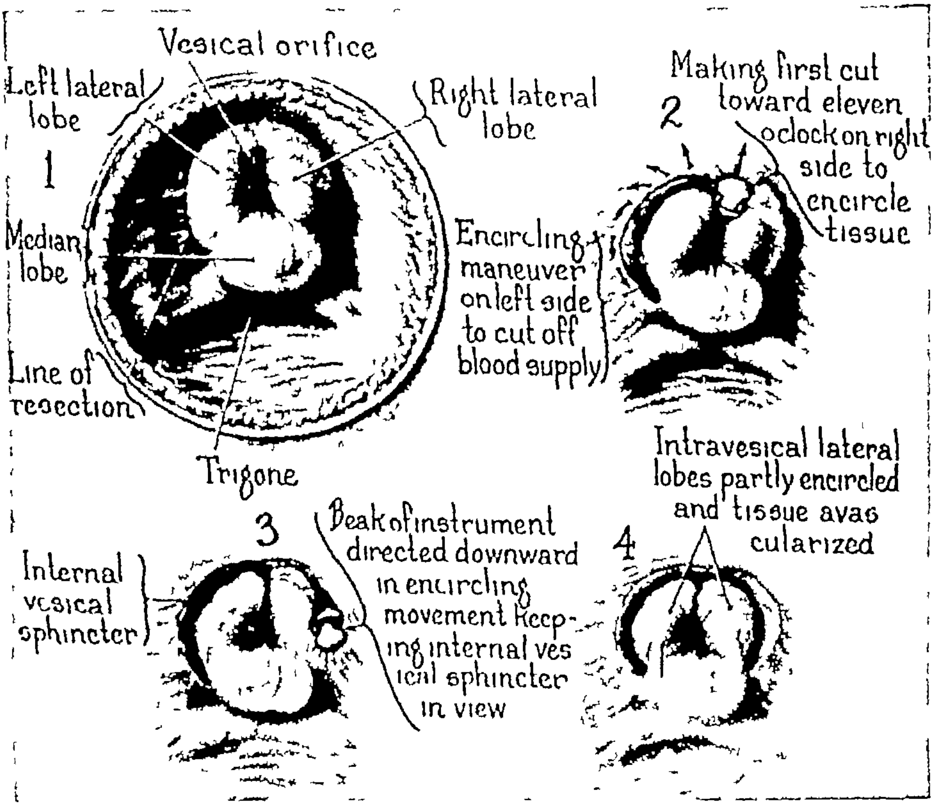
Vesical orifice
Left lateral lobe
Right lateral lobe
1
Median lobe
Line of resection
Trigone
Encircling maneuver on left side to cut off blood supply
2
Making first cut toward eleven o'clock on right side to encircle tissue
3
Internal vesical sphincter
Beak of instrument directed downward in encircling movement keeping internal vesical sphincter in view
4
Intravesical lateral lobes partly encircled and tissue avascularized

FIG 2 Depicting part of avascularizing technique developed by Nesbit (Courtesy of Nesbit, R M Transurethral Prostatectomy Springfield, Ill Charles C Thomas, Publisher, 1943, p 65 )

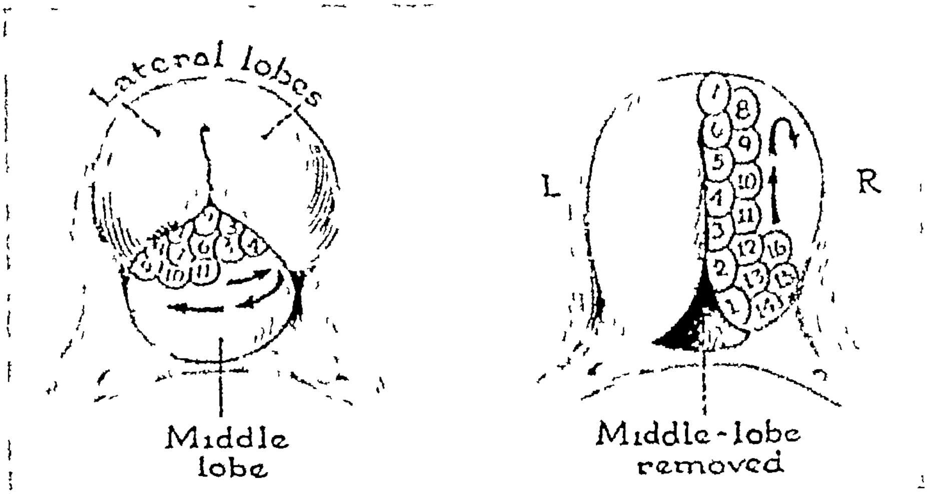

FIG 3 (Left) transvesical view of prostate showing removal of middle lobe Figures indicate order of removal of tissue pieces (Right), removal of lateral lobe (Courtesy of Barnes, R W J Urol 65 603-607, 1951 )

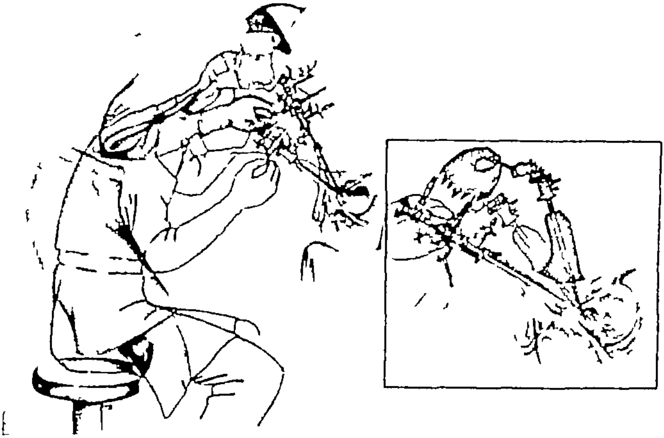

Fig 4 Drawing designed to show movement of sheath with loop extended pressing loop into prostatic tissue by swinging ocular end away from plane of tissue and completing cut with control handle

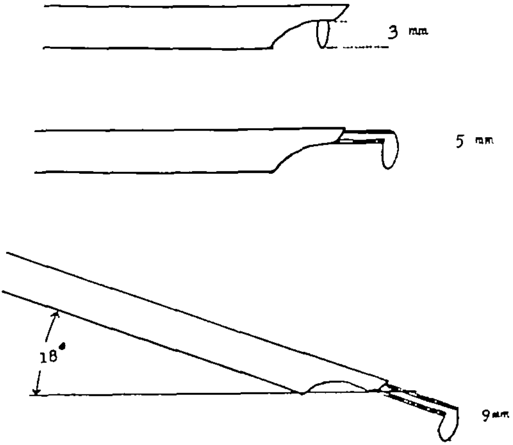

Fig 5 Showing potential depth of cut with loop in various positions

to efficient performance of transurethral prostatic resection In order to obtain satisfactory freedom of movement of the resectoscope, occasionally it becomes necessary to deviate from one's regular plan of resection in order to remove intervening projecting prostatic tissue that is impeding the progress of the operation

OUTLINE OF FACTORS OF JUDGMENT

1) Recognition of tissues encountered in transurethral resection of the prostate

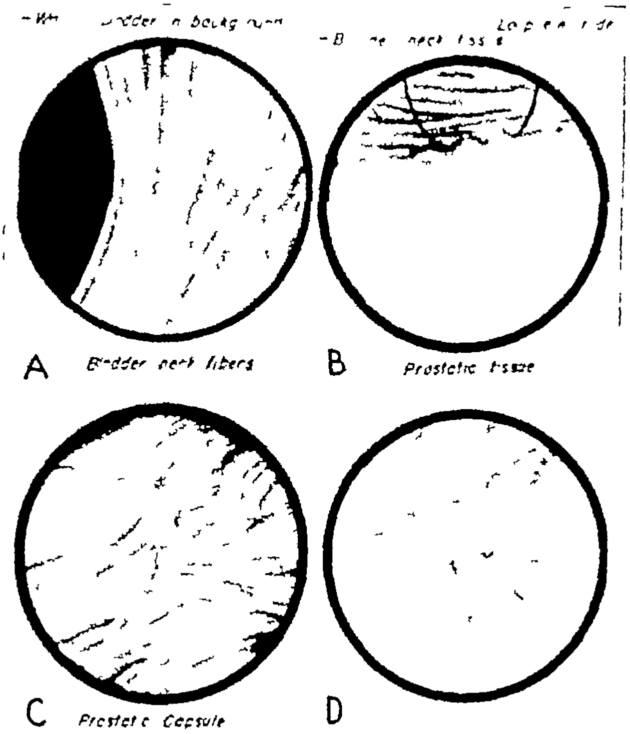

Fig 6 (Courtesy of Barnes, R W and Martin, I E Endoscopic identification of tissue during transurethral prostatic resection J Urol , 62 730-735, 1949 )

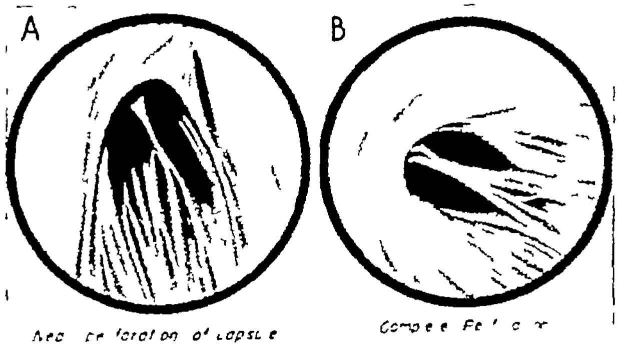

Fig 7 (Courtesy of Barnes, R W and Martin, I E Endoscopic identification of tissue during transurethral prostatic resection J Urol , 62 730-735, 1949 )

- A Bladder neck fibers with wall of bladder in background (fig 6, *A*)
- B Prostatic tissue (fig 6, *B*)
- C True prostatic capsule (fig 6, *C*)
- D False or surgical capsule (fig 6, *D*)
- E Near perforation of capsule (fig 7, *A*)
- F Perforation of capsule (fig 7, *B*)
- G Accordion pleat appearance of contracted prostatic capsule
- H Junction of prostate with membranous urethra identified by wrinkling of mucosa, as described by Barnes and Martin and also by Nesbit

2) Decision to perform perineal urethrotomy based on
    - A Small caliber anterior urethra that inhibits movement of sheath
    - B A short suspensory ligament restricting depression of instrument
    - C A high, large prostate difficult to reach via the anterior urethra
3) In controlling bleeding during prostatic resection
    - A Locate the vessel and coagulate it and avoid coagulating large surface areas
    - B Recognize venous sinus bleeding with low pressure test and don't waste time trying to control this type of bleeding during operation as pressure later will do it
    - C Avoid pushing up blood pressure by drugs used with spinal anesthesia
    - D Postpone final hemostasis until all tissue has been evacuated as the latter can reactivate bleeding
4) Some criteria of completion of transurethral prostatectomy
    - A The four simple cystoscopic rules formulated by Henry S Browne
        1. With the sheath carefully centered and the verumontanum just visible with the foroblique telescope, no tissue should be observed to fall in the open end of the sheath when it is rotated in a complete circle
        2. On examination with the retrospective telescope, the entire circumference at the junction of the operative area and the bladder should show no prostatic tissue projecting into the bladder at any point
        3. On examination of the prostatic cavity no tissue should be seen projecting into it at any point
        4. The verumontanum should be completely visible with the retrospective telescope
    - B If all prostatic tissue is recognized and removed the capsule will be exposed throughout the prostatic fossa
    - C Fill bladder before removal of the resectoscope and with gentle pressure suprapubically, the patient should void with a good stream

## SUMMARY AND CONCLUSIONS

A number of factors have been reviewed, and some of our personal impressions have been expressed relative to the expeditious performance of transurethral resection of the prostate Such an operative procedure that is fraught with so many technical difficulties, and requires so much mechanical and electrical equipment, will, naturally, be affected by many factors, both large and small, and only by careful attention to all of these factors can satisfactory results be obtained

*214 E Harrison Ave , Harlingen, Texas*

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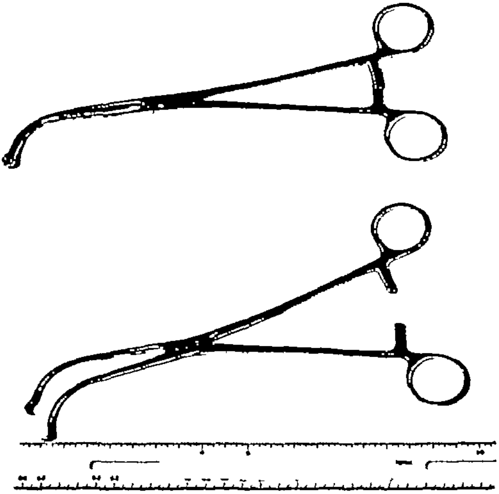

FIG 1

I believe that this ureteral clamp is a definite advantage in ureteral surgery, and that it is a useful addition to the urologist s armamentarium

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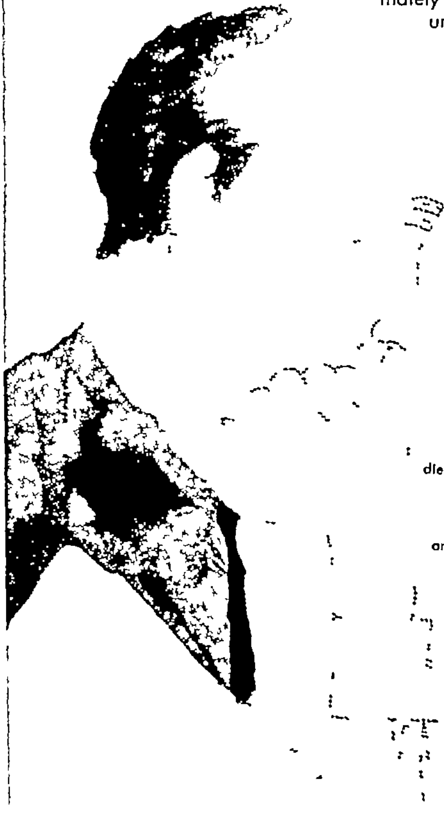

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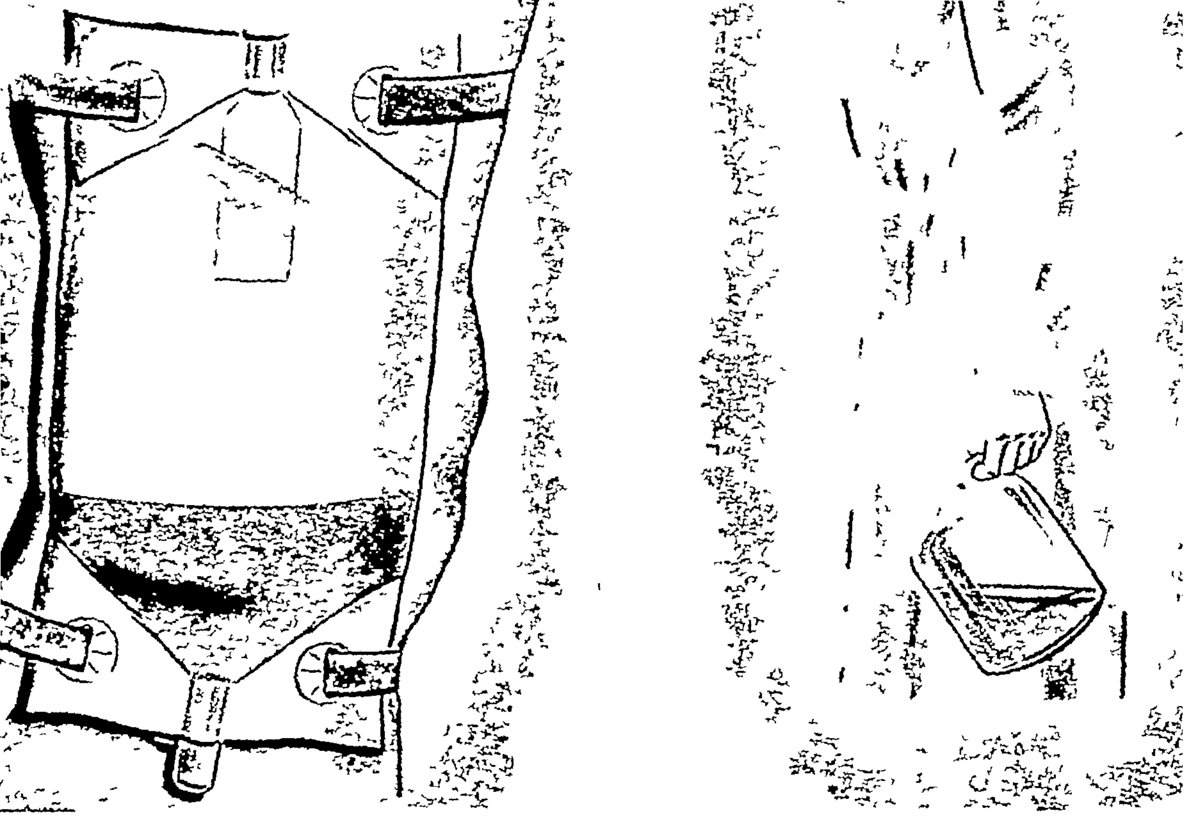

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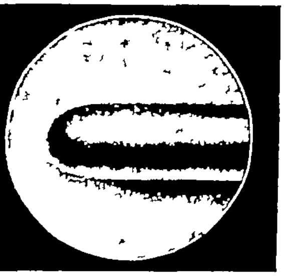

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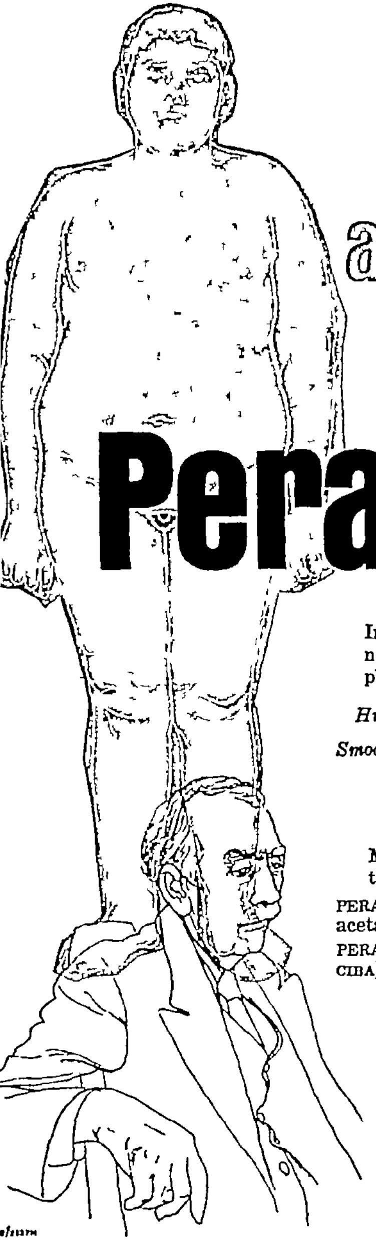

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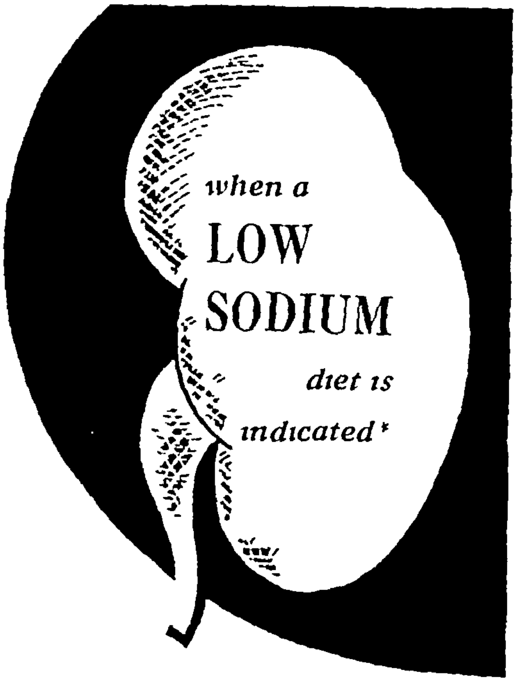

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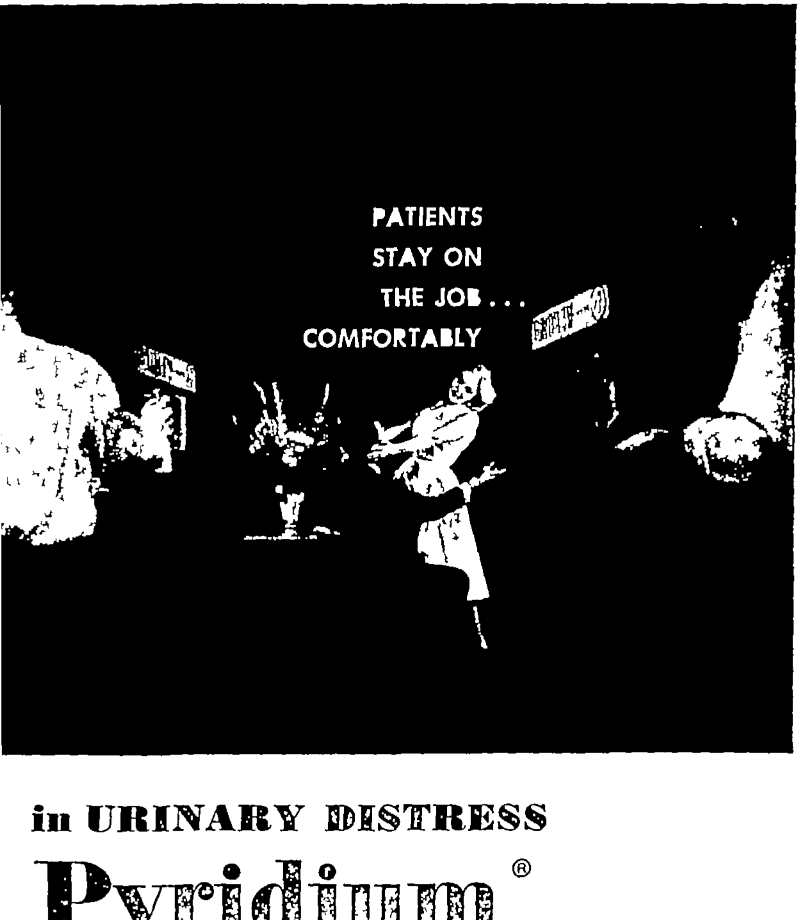

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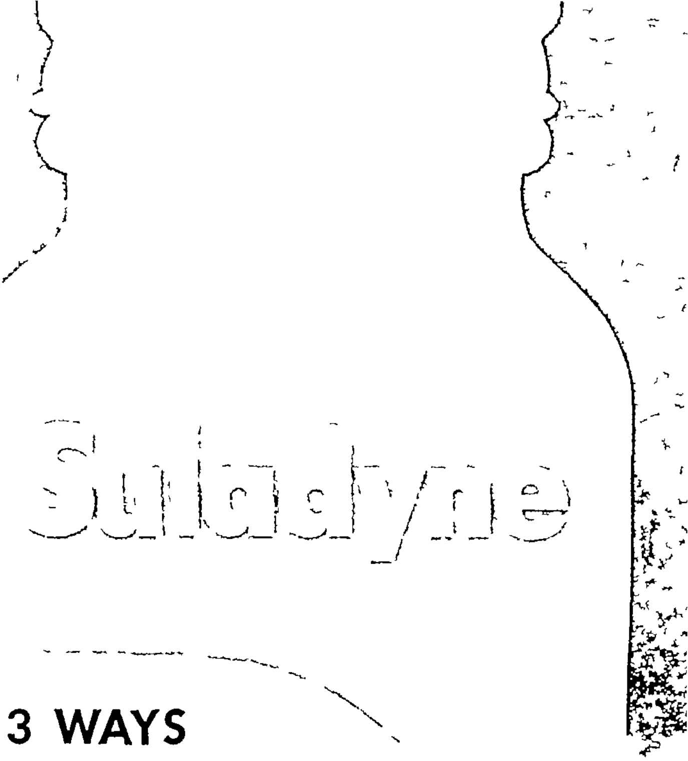

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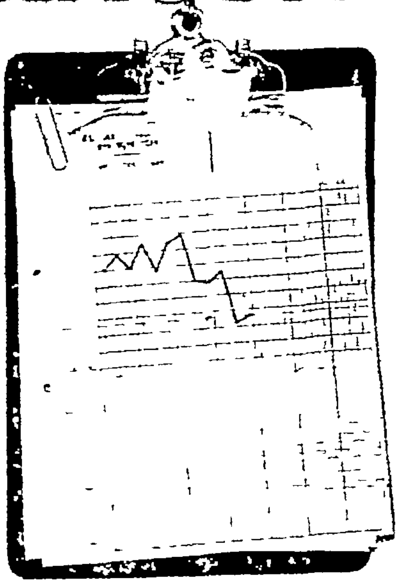

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## CONTENTS

Elective Prostatectomy *G C Prather* 131

Renal Cell and Transitional Cell Carcinomas in Same Kidney *J B Graham and W J Vynalek* 137

Effect of Donor Kidney Homogenate on Survival of Kidney Tissue Homografts in Separated Parabionts *B B Kamrin* 142

Technique to Determine at Operation Area of Renal Parenchyma Supplied by Aberrant Vessel *E N Khoury* 149

Experimental Studies on Reconstruction of Neurogenic Bladder *W C Shoemaker and D M Long Jr* 150

Sertoli Cell Tumor in Infant *D A Culp R G Frazier and J J Butler* 162

On Potential Enzymatic Control of Uric Acid Metabolism *Morris London and A L Finkle* 168

Anorchism without Eunuchism *R D Amelar* 174

Prognostic Significance of Elevated Serum Acid Phosphatase Level in Advanced Prostatic Carcinoma *E J Ganem* 179

New Renal Function Test The Radioactive Diodrast Renogram *C C Winter* 182

Inadequate Sterilization of Cystoscopes *J K Lattimer Michael Kenney, George Rosenblatt and Milton Goldman* 197

Self Managed Bladder Training Device for Tetraplegics *A E Comarr* 200

A Plastic Scrotal Bridge *J S Hirsh* 203

Improved Analgesia with Nisentil and Levallorphan *H A Garnes* 204

Pseudo Water Diuresis in Man *L A Toth* 206

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*Annual Meeting, American Urological Association, Hotel William Penn*
*Pittsburgh, Pennsylvania, May 6–9, 1957*

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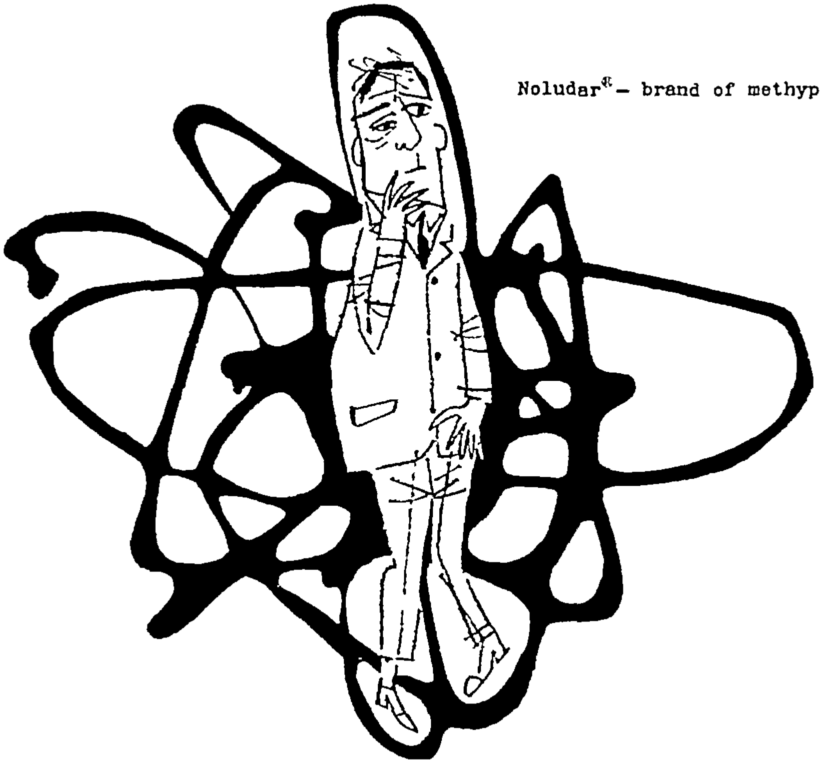

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* E L Prien and B S Walker JAMA Feb 4 1956 pp 355 360
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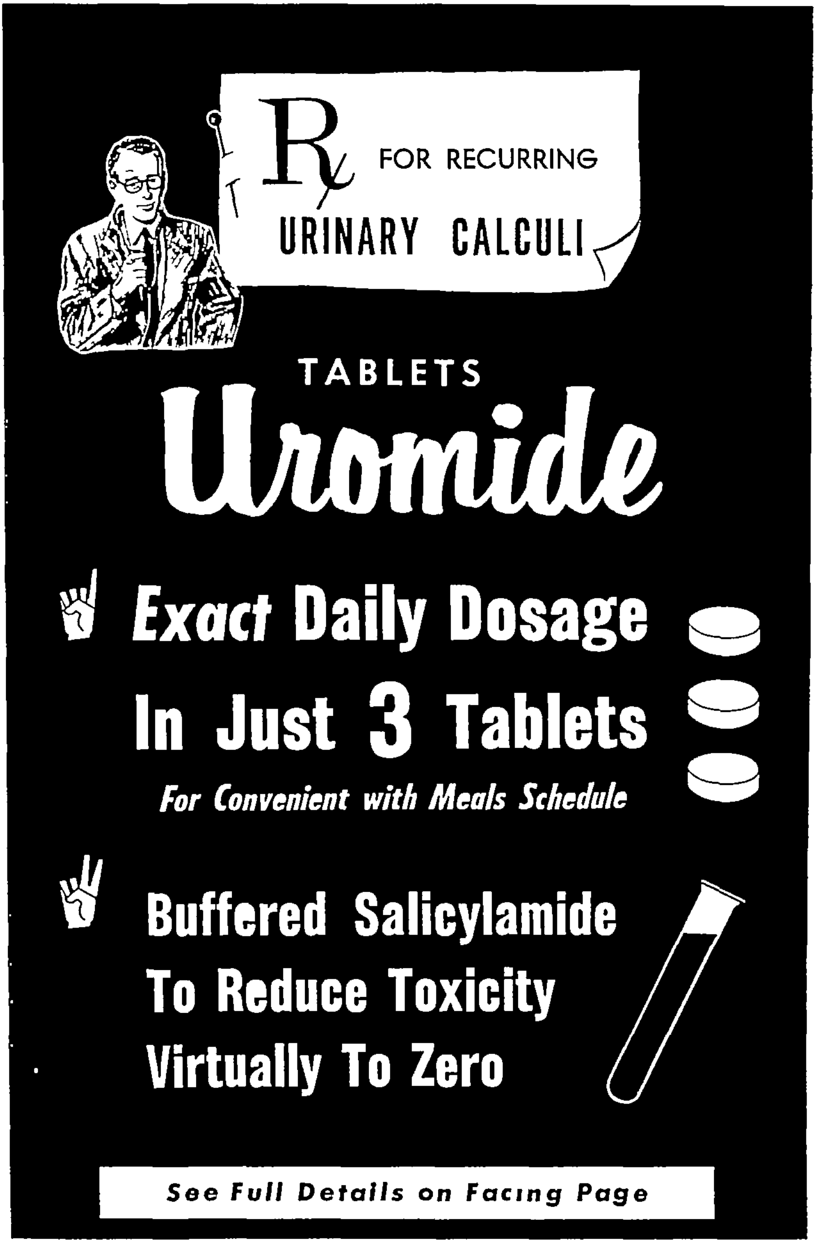

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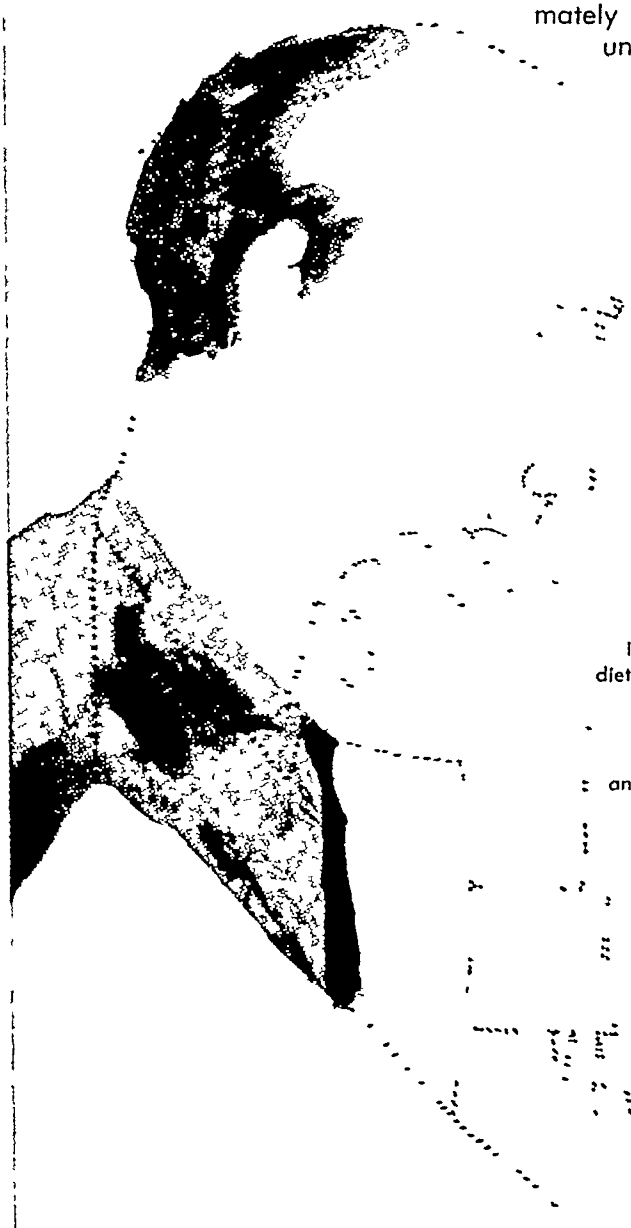

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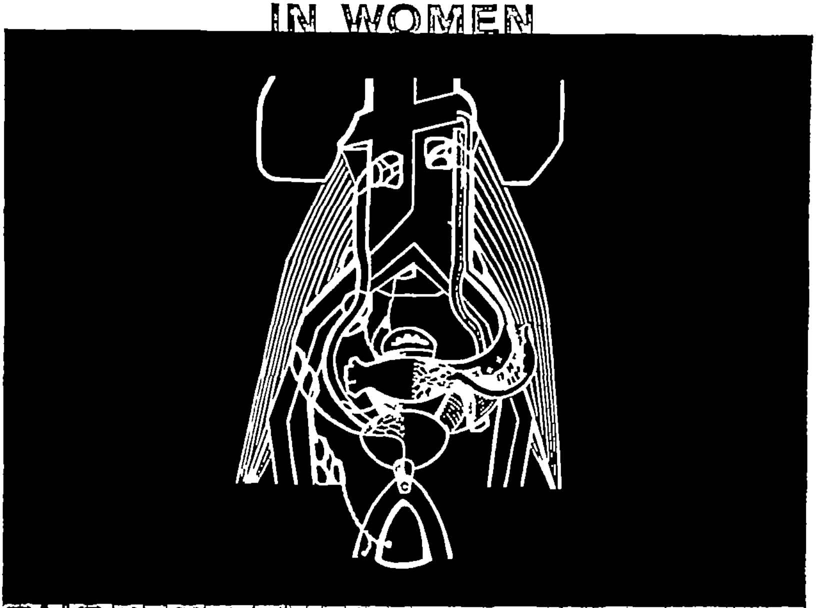

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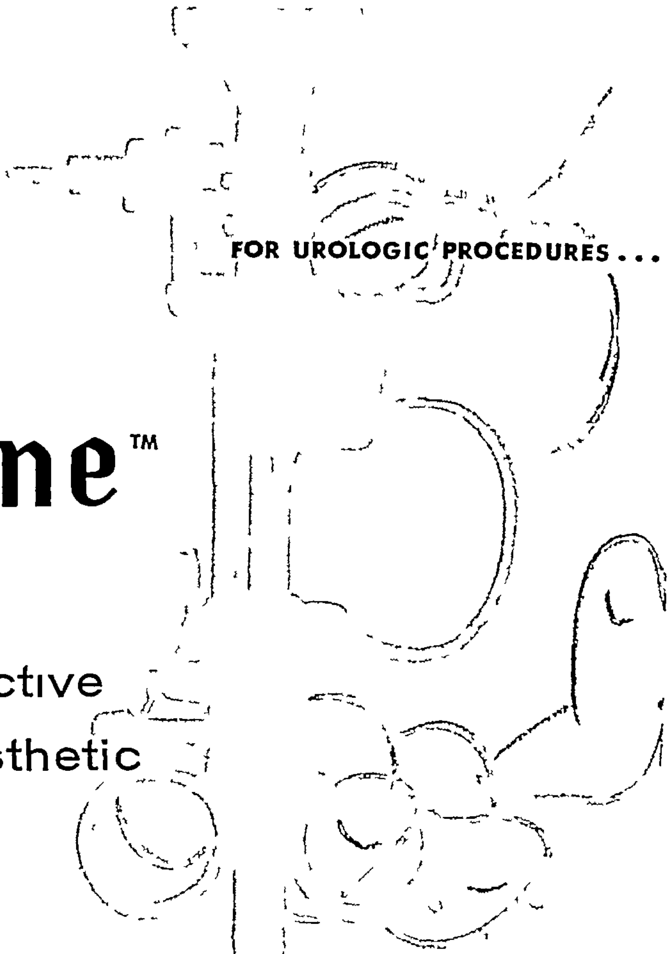

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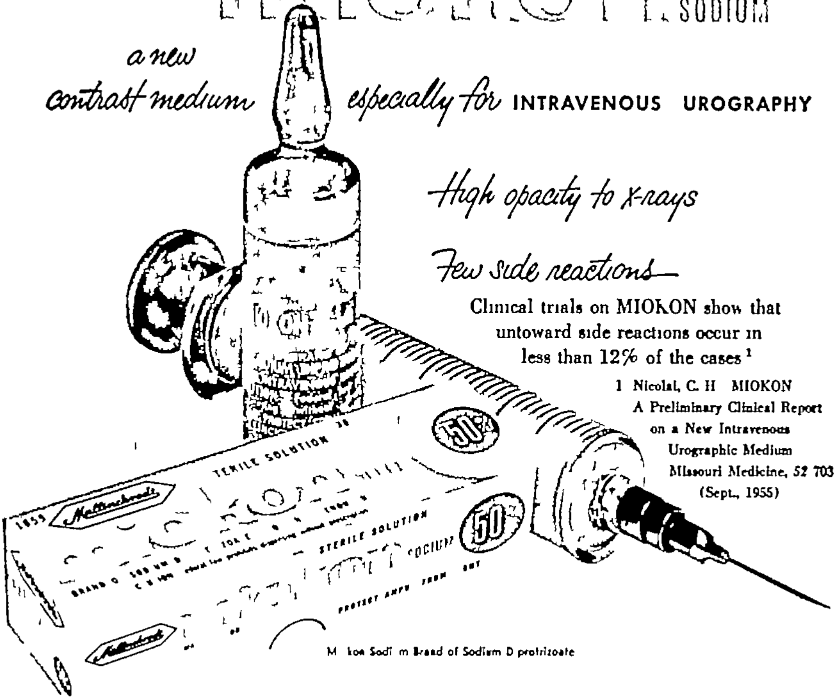

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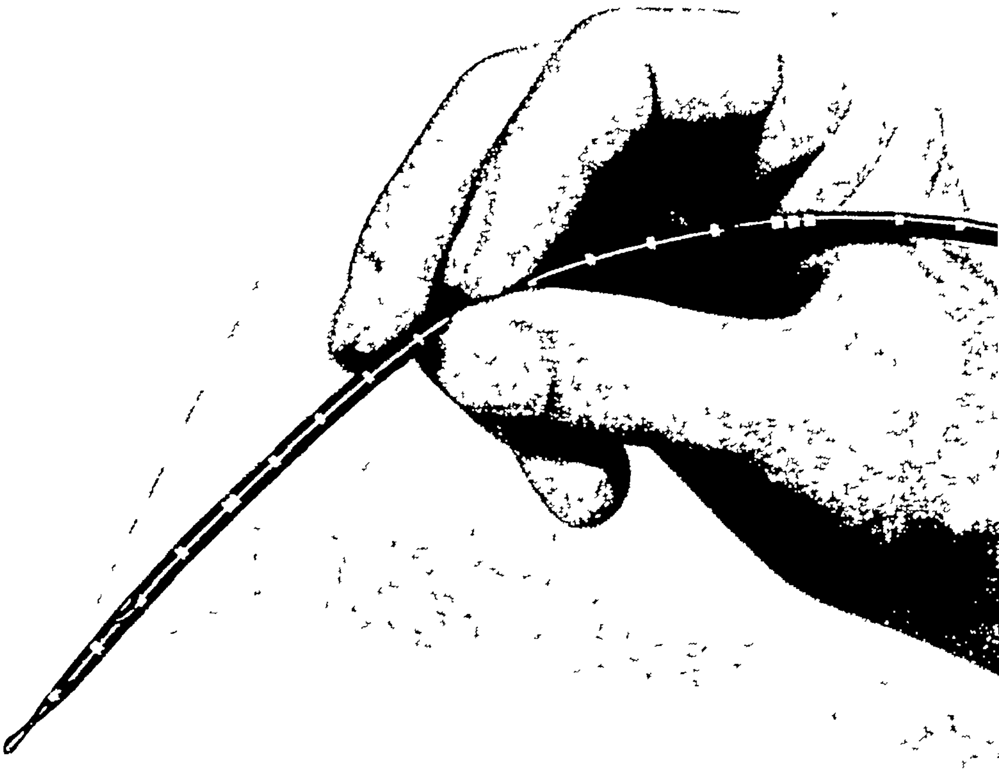

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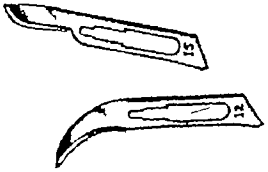

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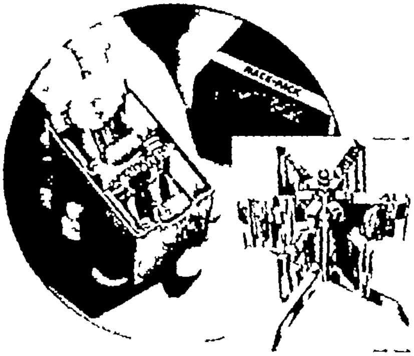

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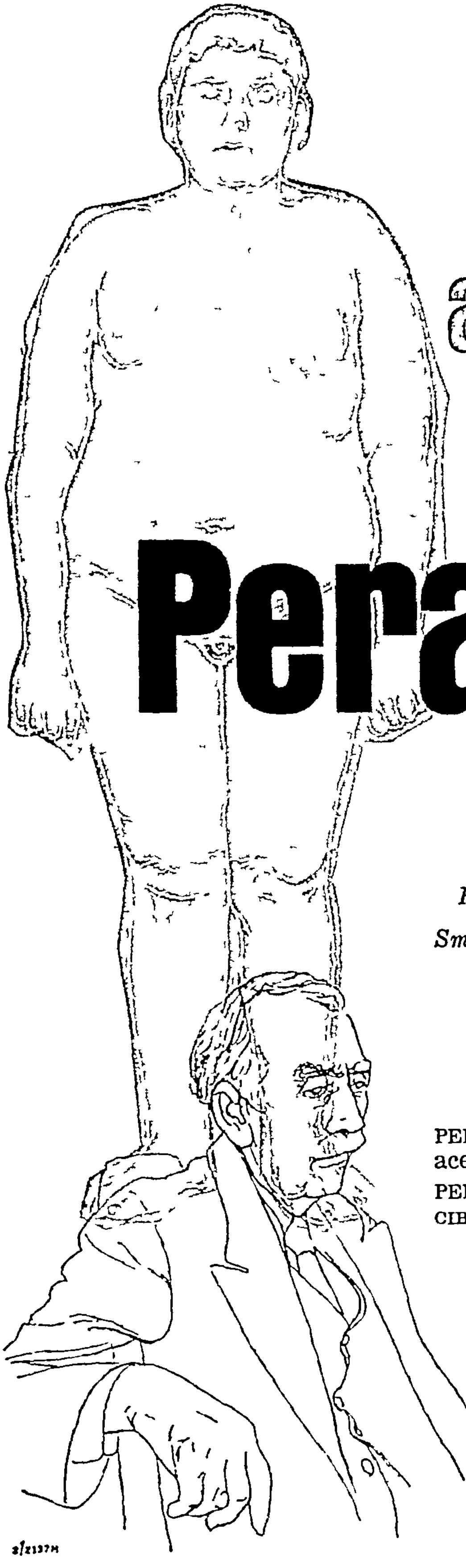

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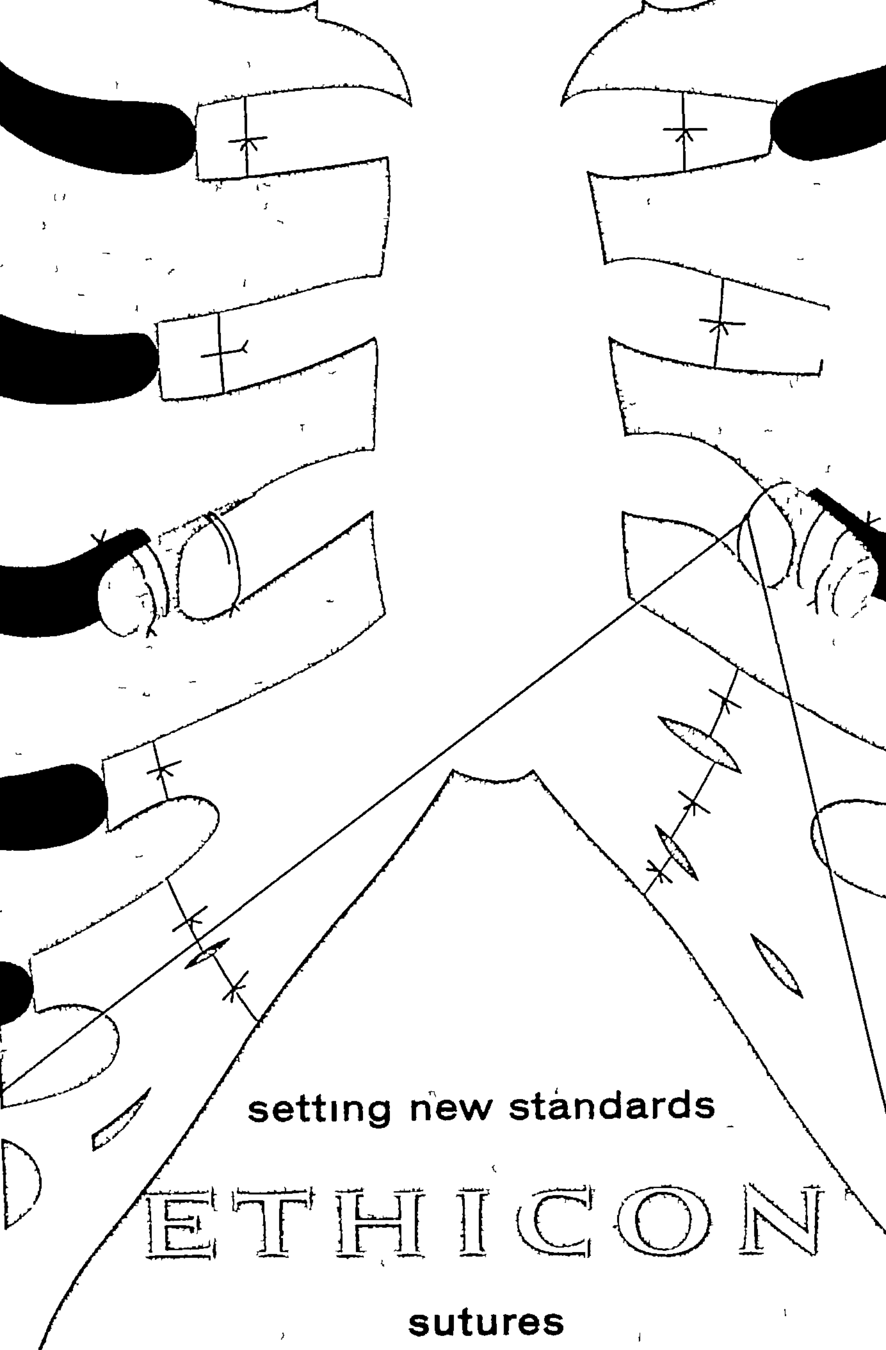

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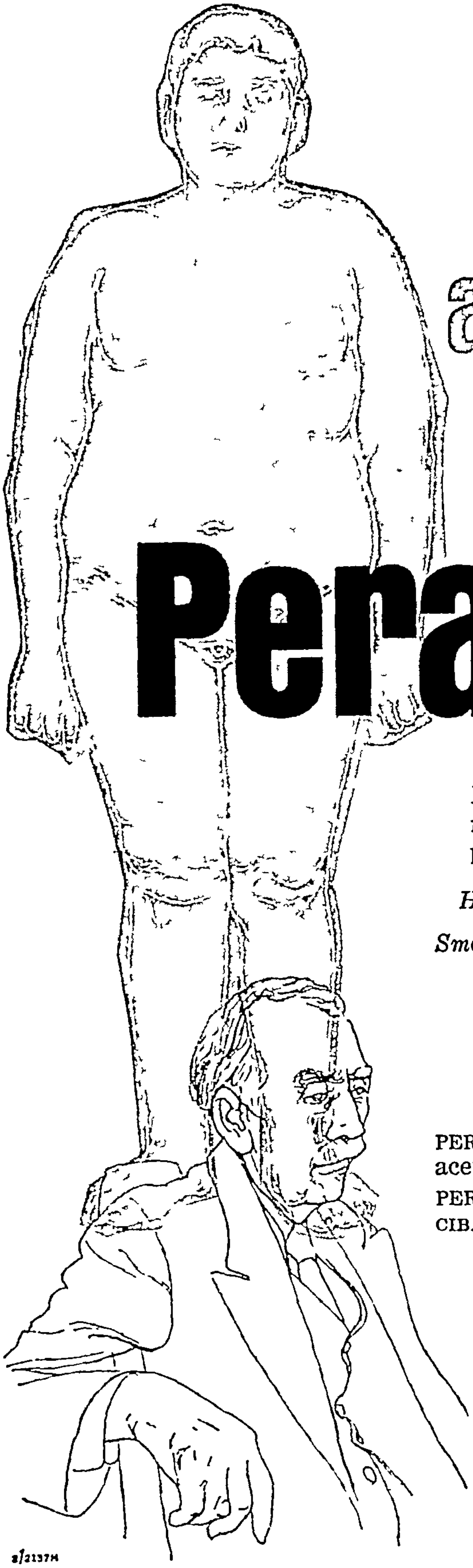

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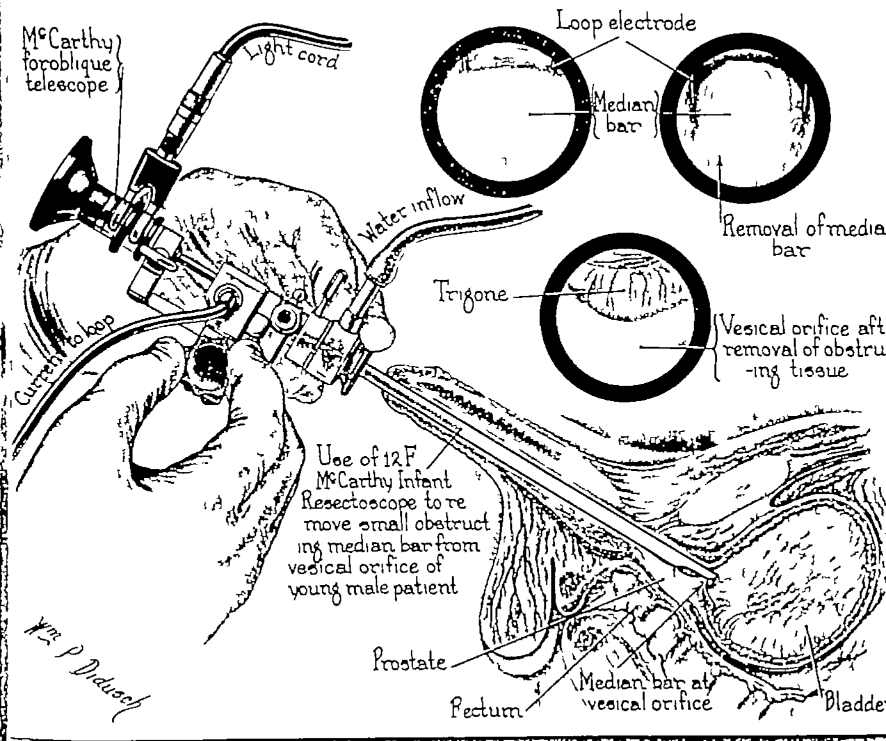
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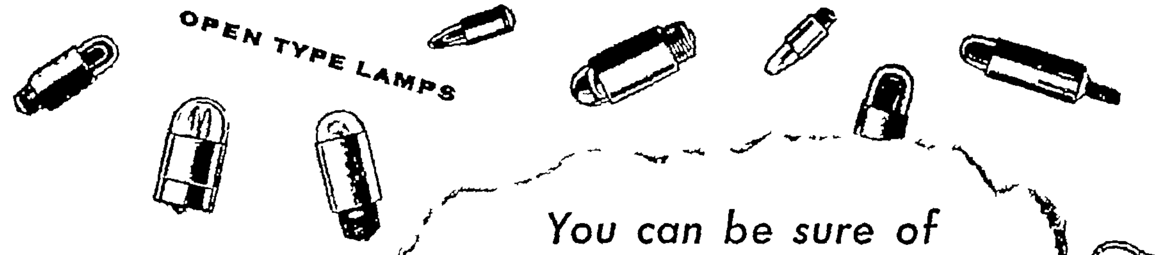

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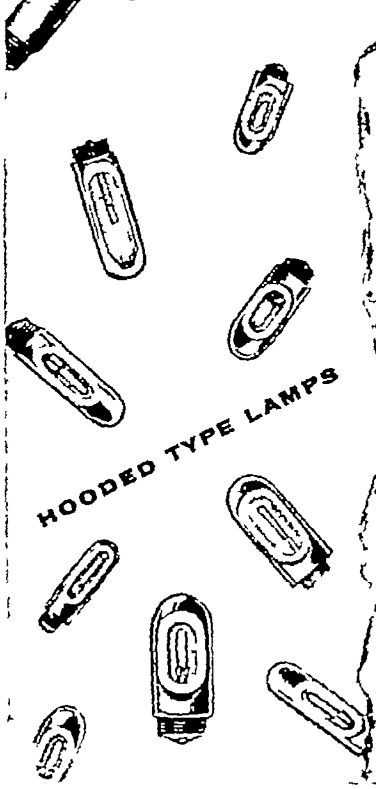

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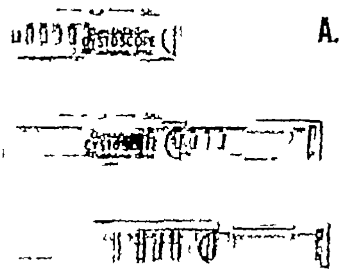

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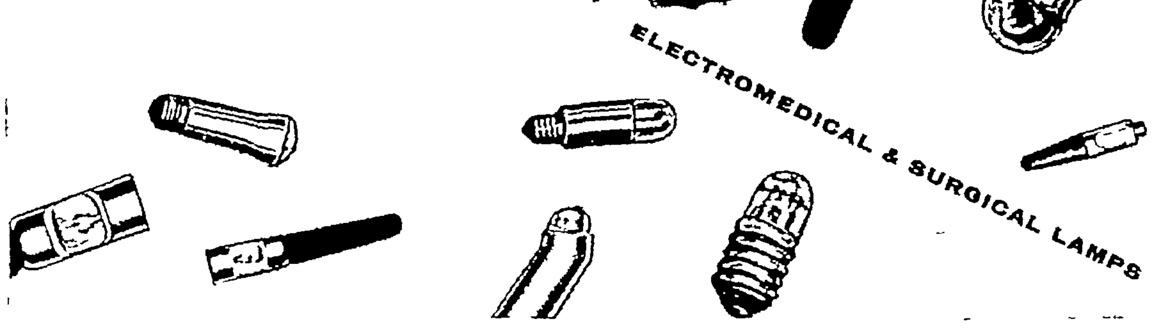

THE JOURNAL OF UROLOGY
Vol 76 No 2, August 1956
*Printed in U.S A*

# ELECTIVE PROSTATECTOMY

GEORGE C PRATHER

There is an old phrase in the theatrical world which says 'If you can't top it, don't follow it' However, when you or I find ourselves as president of the American Urological Association, we realize that we are obliged to follow many outstanding predecessors whom we cannot top

One of the duties of this office is a presidential address Probably in the past none of your distinguished presidents has ever had difficulty in selecting the title for his paper or in composing the substance of his remarks In former years subject matter has been varied to include reports on the growth and record of this Association suggestions for improvements in its organization and operation, inspirational commentaries dealing with the life of doctors as a group, and discussions of the development of urology, emphasizing the trends in the education of those training for a surgical specialty All of these presidential addresses have been capably given in a mature and philosophical manner consistent with the great dignity and accomplishments of the several speakers I find myself perhaps on the fringe of this philosophical era of man's life but not wise enough at this time to offer valid proverbs which would hold for the future

Perhaps I should have reviewed the financial status of the A U A for you today, but having heard the roar of the tides in the nature of direct and indirect remarks from the membership over a period of 7 years in regard to the mountains of money concealed in the treasurer's office, I decided to bow out from that responsibility as quietly as possible Furthermore in the new and capable hands of our present treasurer everything will be better and my remarks regarding finances would only disturb a pseudoantibiotic mold which would prove to contain none of the therapeutic value that we hope to be curative

I have therefore decided upon a clinical topic, elective prostatectomy about which I have found many divergent opinions—very positive opinions in fact, made in writing from your capable colleagues throughout this country The quotations that I will mention were in reply to some questions I raised about the subject by way of the Urologists' Correspondence Club

One reason for my considering this matter at this particular moment is the tradition that there are no discussors of the president s address Therefore the speaker has temporary immunity from those who disagree with the doctrine expressed

Another, and more important reason for choice of this subject is that after the development of urology as a surgical specialty for 50 years, one should expect some agreement as to the indications for probably the most common surgical procedure that we are required to perform

Of course there is no disagreement as to the indications for prostatectomy in patients with acute urinary retention with a large bladder residual with recur

---

Presidential address read at annual meeting American Urological Association May 30 1956 Boston Mass if it is needed for further use in the office or in hospital He has found you gentle and expert in its use, and, as for others less expert than yourself whom he may meet under similar circumstances, he will have harsh words for them and greater esteem for you

Catheterization will also be informative to the urologist In the first few moments he can tell whether the patient is hypersensitive and likely to be difficult in hospital where catheters and other apparatus are a certainty, or whether the patient is tolerant and perhaps factual in the description of his symptoms The catheter can be used to discover any obstruction in the distal urethra if it is present—rather useful information before any removal of the prostate By delicate touch one senses the degree of spasm at the region of the external sphincter, the relative ease or difficulty with which the catheter passes through the prostatic urethra and bladder neck By the flow of urine through the catheter into a basin with and without the use of concurrent suprapubic pressure one also gets an impression about the tonicity of the bladder wall Furthermore, the two-way test of bladder residual can be done by instilling 150–180 cc of irrigating solution through the catheter and measuring the amount that the patient voids as soon as he stands The patient demonstrates the efficiency or inefficiency of his bladder to himself as well as to you The data serve as a baseline for comparison at a later date, if need be

In contrast to one urologist who replied that "residual urine is not a fixed quantity as six eggs are one half dozen today, tomorrow, and the next day," I have found over the years by quarterly, semiannual, or annual examinations that in most individuals in whom I do not believe prostatectomy immediately indicated, bladder residuals have been reasonably constant within a 10–30 cc variation

Although there will be exceptions to the need or advisability of catheterization to demonstrate the amount of bladder residual, I believe it is informative both to the patient and to the physician when done with a clean and gentle technique by the urologist himself

In order to advise a patient properly about elective prostatectomy, we must have some conception about whether early symptoms are certain to progress, whether they may remain at minimal level for an indefinite period of time, or whether they may improve

Let us rule out the patient with symptoms of bladder irritability which are caused by urinary tract infection (not on the basis of prostatic obstruction), those with acute or chronic prostatitis, and those who improve partially or completely with internal prostatic massage even though neither the urine nor prostatic secretion shows infection

In other words, is the patient with symptoms of early benign prostatic obstruction destined to have progressive change for the worse with time? Opinion on this point would appear important if one is to advise the patient as to the need of surgery Of the well-known urologists throughout the country who have replied to me on this point, all agree that slow progression of symptoms is the most common course of the disease However, about 70 per cent are also aware, through their personal experience that the level of symptoms or obstruction may well remain static for a long time I offer you some of the quoted opinions on this point, "The progression of symptoms, I believe to be constant, but so slow in some cases that much time may elapse before they change from minor to major symptoms," "the great majority of prostatic lesions are progressive—only a small number seem to remain stationary," "prophylactic operation is a financial procedure in my book " "it has been my experience that relatively early symptoms and signs of prostatism are only very slowly progressive in most cases," patients should not be operated upon just because they have an enlarged prostate a few obstructive symptoms and very little or no residual urine," "as you know I am in favor of early surgery and radical if indicated,' "my conception is that relatively early symptoms and signs of prostatism usually become progressive some remain static for quite awhile others subside spontaneously but recur later " "it has been my experience that the symptoms of benign hypertrophy of the prostate follow such a variable course that operation is not warranted in the anticipation of future difficulty "

In the remarks quoted above, and from other replies not quoted, one hears very little of an attitude that I seem to have heard frequently a few years ago to the effect that operation should be done at once before the patient's general condition becomes unfavorable at a later date I would say that those who do advise an early surgical attack on the prostate will not have a guilty conscience if they change their position and take refuge in the quoted experiences of those who have just spoken

Another important point upon which we should have an opinion if we are to advise patients correctly is, will renal function deteriorate in a patient with an obstructing prostate who carries an uninfected residual of 60 cc or less? We have very meagre information on this important point The few who answered this question said "No " More common was the failure to answer, or as one honest reply stated, "I do not know how long a time a patient has to carry residual urine to affect renal function Some have partial retention for a long time with no apparent ill effect and others will have nitrogen retention with a fairly short history '

I would like to offer personal comment on the question Perhaps we as urologists having primary attention centered on the prostate, and knowing that a large residual of long duration has been proved on many occasions to be responsible for poor renal function, tend to incriminate the prostate too often in the man of prostatic age who has minor symptoms or a small residual Let us realize that poor renal function can occur as the result of nephritis, diabetes, heart disease, or circulatory changes in the kidneys which may have preceded or may be concurrent with the prostatic symptoms If some type of systemic disease is responsible for poor renal function I suppose it is unlikely that either preoperative drainage of the bladder or prostatectomy will improve the renal situation

The lack of reliable information as to the amount and duration of residual urine necessary to damage renal function temporarily or permanently is unfortunate As clinicians we need an answer As investigators we have been lax in studying this very important point

Two of the common symptoms often associated with early prostatism are frequency and nocturia If the patient has no urinary infection, no prostatitis, and a residual of 60 cc or less, are these symptoms improved by prostatectomy? How do you explain the physiology of these symptoms to the patient? In answer to the first question, 60 per cent of those who replied said, "Yes, prostatectomy would be beneficial" Forty per cent said, "No" In explanation of frequency and nocturia as a symptom in the prostatic suspect as we might call him, two urologists from the middle west emphasized interstitial cystitis as a condition in the male which is frequently present as a cause of symptoms The opinion that the amount of bladder residual is larger at night was offered to explain nocturia Spasm of the prostate was mentioned by one Another said the cause of symptoms was not understood One admitted, "To be perfectly frank, I do my best not to be pushed into a corner where I have to try to explain to the patient" One friend of mine and I have a possible explanation of nocturia under these circumstances We believe either that vascular changes in the kidneys result in a delay in output of urine after intake of fluid during the day, or that a renal situation exists in which kidneys produce urine in more or less constant volume per hour during the 24 hours, rather than by a schedule of increased output followed by a period of rest Certainly if the renal condition is a factor in the nocturia, prostatectomy will not necessarily eliminate the symptoms Once again, there appears to be a chance for valuable study on some of the fundamentals of the urinary tract and its association with prostatism

In addition to the description and evaluation of specific symptoms and findings already mentioned, the conscientious urologist will of course carefully evaluate the patient as an individual in regard to general health, probable length of life and happiness unoperated, will consider the availability of urological care at the patient's place of residence and occupation, and will give due weight to the attitude of the patient toward a surgical or medical program

In summary, the urologist has a definite responsibility to those patients who come to him with symptoms consistent with mild prostatism He should obtain pertinent factual data for justification of his point of view, data which can be used for comparison at a later date if required He should weigh the probable risk of operation against the probable benefit

On reflection, it is evident that there is a chance for some study of fundamental and practical matters relative to prostatic disease—problems which should be solved if possible, now that our specialty is starting on its second 50-year period I admit my inability to answer dogmatically the many questions that can be raised regarding elective prostatectomy and the various important side issues connected with the subject These remarks have therefore been made to you as being provocative rather than definitive

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# RENAL CELL AND TRANSITIONAL CELL CARCINOMAS IN THE SAME KIDNEY

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The purpose of this paper is to report the occurrence of an unusual combination of primary tumors in a surgically removed kidney One lesion was a papillary transitional cell carcinoma of the renal pelvis, and the other a renal cell carcinoma of the upper pole Each is common enough in its own right, but their coincidence has been previously reported only 9 times (table 1*)

Our patient was a man aged 61 whose only complaint was gross total, painless hematuria that had occurred 2 months previously Excretory urograms at that time were reported to show a stone in the left renal pelvis The remaining history and the examination were not pertinent Our cystoscopic findings were normal, but we interpreted the retrograde urograms as representing either blood clots or papillary tumor in the left renal pelvis (fig 1) Laboratory studies and a chest x ray were normal

The left kidney was explored through a lateral subcostal incision The renal pelvis was opened and found to contain papillary tumor (fig 2, *A*) A nephrectomy with removal of the upper 15 cm of ureter was performed An unexpected mass was found in the upper pole On section, this mass was typical yellow-orange renal cell carcinoma (fig 2, *B*) The patient was well enough to be discharged on the eighth day Two months later, through a Gibson incision, removal of 10 cm of the retained ureter and a 3 cm segment of the bladder was done as a second stage procedure No tumor was found in the ureter or bladder

Pathology report (Dr B H Neiman) "The specimen consists of a kidney weighing 167 gm Present also is the renal pelvis and 15 cm of the left ureter At the ureteropelvic junction there is a papillary mass measuring 2 cm in diameter The underlying wall of the renal pelvis is smooth on the outside and apparently not infiltrated On the upper pole of the kidney there is a circumscribed and encapsulated, mottled, yellowish red tumor measuring 6 by 4 by 4 cm One portion of the tumor is quite fibrous and reveals small cysts measuring up to 1 5 cm in diameter Another portion of the tumor shows a soft, yellowish, mottled appearance The remaining kidney shows a brownish color with regular markings

Microscopic sections from the tumor in the upper pole (fig 3, 4) show that it is separated from the kidney parenchyma by dense bundles of connective tissue The tumor is composed of large cells with clear cytoplasm The cells seem to be in a matrix of delicate reticulum so that very little interstitial stroma is present between the tumor cells In some places the nuclei are somewhat larger slightly irregular and hyperchromic For the most part the nuclei are small

"Sections taken from the tumor of the renal pelvis (fig 3, *B*) reveal papillary

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* The followup period is based on personal communication with the authors

the literature

| | ymptoms | Operation | Pathology | Survival |
|---|---|---|---|---|
| 1 Graves and Templeton J Urol, 5 517, 1921 | Man age 52<br>Total hematuria | Nephrectomy<br>Ureterectomy (2 stages) | Papillary carcinoma of renal pelvis plus hypernephroma | Small papillary bladder tumor coagulated 5 mos after nephrectomy, well 7 yrs later |
| 2 DeVries Am J Surg, 10 187, 1930 | Man, age 57<br>Back pain, 4 yrs<br>Hematuria, 1 mo | Division of isthmus<br>Nephrectomy | Hypernephroma, papilloma, and stone in horseshoe kidney | Metastases to skull and femur, treated with x ray and leg amputation, alive 7 yrs after surg |
| 3 Wildbolz Proc 5th Cong Int Soc Urol, vol 2, p 163, 1933 | | Nephrectomy | Papillomas, renal pelvis Hypernephroma upper pole | |
| 4 Balch J Urol, 33 138, 1935 | Man, age 63<br>Hematuria, 3 mos | Nephrectomy<br>Ureterectomy (upper 2/3) | Papillary carcinoma of inferior calyx plus hypernephroma lower pole | Died 11 yrs later of myocardial infarction, no evidence of recurrent tumor |
| 5 Dick Bull Lahey Clin, 2 231, 1942 | Woman, age 51<br>Hematuria, 1 mo | Nephroureterectomy | Papilloma renal pelvis Renal cell carcinoma 0 5 cm diameter | |
| 6 Melicow J Urol, 54 186, 1945 | Man, age 65<br>Vesical papilloma treated 11 yrs previously | Nephrectomy | Papillary epithelioma of renal pelvis, grade 2 Clear cell carcinoma of kidney | |
| 7 Macalpine Brit J Surg, 35 131, 1947 | Woman, age 72<br>Hematuria, 7 mos | Nephrectomy<br>Ureterectomy (2 stages) | Papillary carcinoma renal pelvis and adenocarcinoma of kidney, carcinoma lower ureter and bladder 1 yr ltr | Died 21 mos after nephrectomy with active bladder cancer |
| 8 Rupel and Sutton J Urol, 63 187, 1950 | Woman, age 58<br>Flank pain, 5 wks<br>Hematuria, 5 days | Nephrectomy | Papillary carcinoma renal pelvis grade 3 plus adenocarcinoma of kidney, grade 2 | Died 3 mos postoperatively with metastatic adenocarcinoma |
| 9 Kline et al J Urol, 73 961, 1955 | Sex not stated, age 47<br>Hematuria, dysuria and frequency 4 mos | Hemicystectomy & Neoureterocystostomy, nephroureterectomy (2 stages) | Papillary transitional cell carcinoma of the bladder and renal pelvis plus papillary renal cell adenocarcinoma of parenchyma of the lower pole | |
| 10 Graham and Vynalek J Urol, 76 137, 1956 | Man, age 61<br>Hematuria, 2 mos | Nephrectomy<br>Ureterectomy (2 stages) | Papillary transitional cell carcinoma renal pelvis plus renal cell carcinoma of upper pole | No evidence of recurrence 6 mos after nephrectomy |

Fig 1 Retrograde pyelogram shows filling defects in renal pelvis

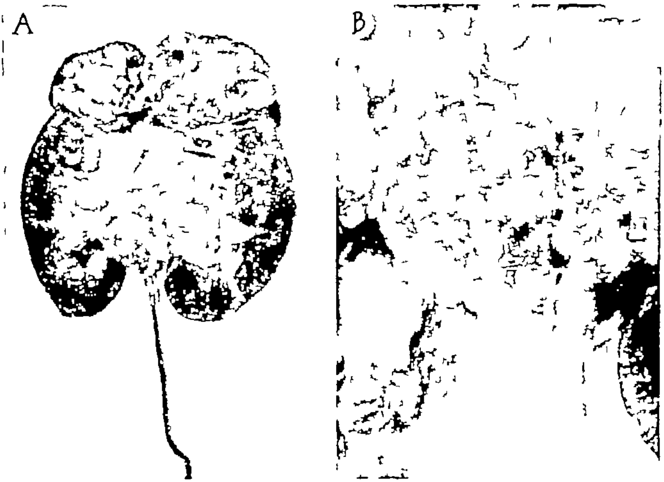

Fig 2 A separate and dissimilar carcinomas of upper pole and ureteropelvic junction *B* close-up photograph of papillary carcinoma of renal pelvis

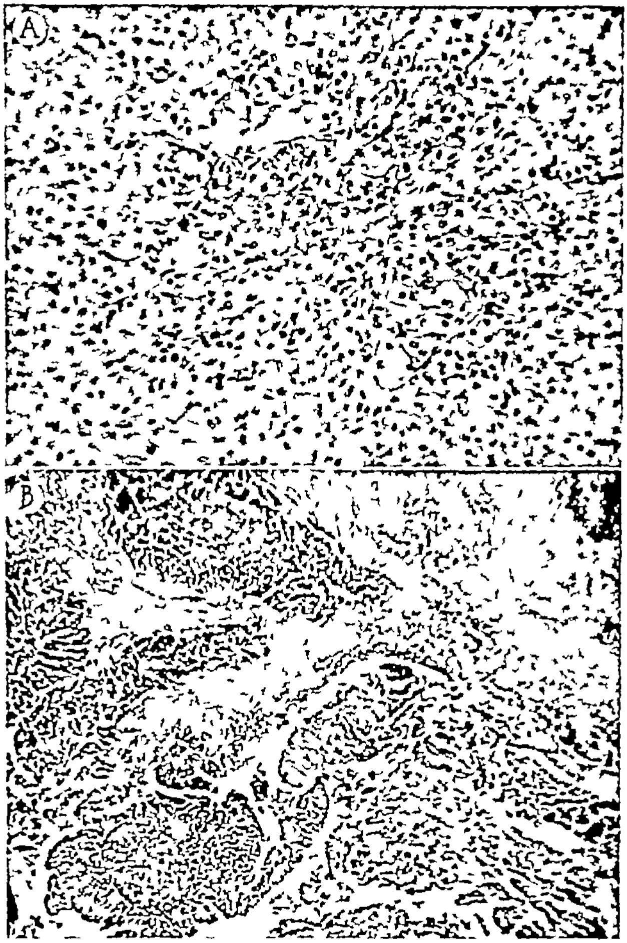

FIG 3 A, section from upper pole tumor to show renal cell carcinoma (×250) *B*, section from tumor of renal pelvis to show papillary transitional cell carcinoma (×145)

arrangement of large transitional type cells The nuclei of the cells are often large, hyperchromic, and irregular At the base of the tumor is seen an invasion of the underlying renal pelvis

"Diagnosis Hypernephroid carcinoma, left kidney Papillary transitional cell carcinoma, left renal pelvis

"Comment of pathologist Since each of these neoplasms is of different histologic structure, it can be labeled a multiple type carcinoma "

### DISCUSSION

The etiology of renal tumors remains obscure Experimental evidence of virus-caused adenocarcinoma in the kidney of the tree frog[1] and papilloma in bladder of rabbits exists Adenomas can be induced in the rabbit kidney with cholesterol,[2] and adenomas probably can be precursors of adenocarcinoma [3] The coincidence of dissimilar tumors, as occasionally reported in the urinary tract, could be explained by most of the existing theories of tumor etiology These theories include embryonic, chemical, viral, and hormonal origins

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[1] Lucké B Am J Cancer 34 15, 1938
[2] Leary T Arch Path 50 151, 1950
[3] Cabot H and Middleton H W Trans Am Assn G U Surg , 31 91, 1938

An interesting diagnostic feature of many of the cases here presented is that the papillary tumor of the renal pelvis had bled, and this called attention to a kidney containing a relatively small clear cell carcinoma coincidently removed

The treatment of choice for papillary carcinoma of the renal pelvis continues to be nephroureterectomy including the segment of bladder containing the intramural ureter and its orifice[4] Subsequent cystoscopic examinations must be performed

## SUMMARY

The tenth instance of renal cell and transitional cell carcinomas in the same kidney has been reported A tabular review of the literature is included

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[4] Kimball, F N and Ferris H W J Urol , 31 257 1934

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# THE EFFECT OF DONOR KIDNEY HOMOGENATE ON THE SURVIVAL OF KIDNEY TISSUE HOMOGRAFTS IN SEPARATED PARABIONTS

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In the light of present experimental knowledge, one or more of the following conditions must be present to permit the retention and possibly the survival of the kidney homograft In humans, the donor and recipient must be uniovular twins In animals, the kidney homografts must be first transplanted to the anterior eye chamber or brain and after stromatization, transplanted elsewhere in the body (Greene), or reciprocal homografts may be exchanged between albino rats in continuing successful parabiosis (Kamrin and Kamrin, '54 and '55) Animal hosts have also been conditioned to permit the survival of homografts by the prior introduction of adrenal hormones (Billingham, Krohn and Medawar, Krohn, Toolan), the pregnant state and placental hormones (Heslop, Krohn and Sparrow), or by exposing the recipient fetus to donor cells (Medawar)

The use of donor homogenates to facilitate the survival of tumor homografts in mice has been reported in the literature (Fink, Snell and Kelton, Kaliss, et al, '50, '52, '54, '55) The benefits of these procedures are assumed to be due to defensive neutralization of the homograft antigen by prior stimulation of such response by the use of the immunizing injections (Kahn) It is also apparent from the literature (Flexner and Jobling) that living cells are not a necessary constituent of such homogenates

Previous studies on kidney tissue homotransplantation to the kidneys of single, parabiont and separated formerly parabiosed albino rats disclosed that only during continuing successful parabiosis do such transplants remain viable (Kamrin and Kamrin, '54 and '55) Kidney tissue homografts transplanted to single littermates always terminated by the eleventh day in complete necrosis and sloughing of the graft Simultaneous parabiosis and kidney tissue homotransplantation with subsequent separation of the operated parabionts at varying periods up to 30 days permit stromatization of the graft although the parenchymal cells degenerate (unpublished data) Similar findings result when reciprocal homotransplantation is performed *after* the separation of the successful parabionts (Kamrin, '56) Such grafts do not retain living parenchymal cells although the basement membrane outlines of the glomeruli and tubules are evident as well as a prominent vascular network The preceding data strongly suggest that the state of continuing parabiosis supplies such necessary factors which tend to neutralize or inhibit the antigenicity of the kidney tissue homografts and permit their survival The data further suggest that separating the animals after successful parabiosis interrupts the constant elaboration of unidentified factors and leads to the loss of viability of the graft although the transplant becomes stromatized and vascularized

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Investigations by Pressman suggest that there are specific kidney antigens and that a kidney homogenate should stimulate specific donor kidney antibody formation for the neutralization or destruction of the antigens Preliminary data derived from paper electrophoresis studies of the blood plasma of single and parabiotic albino rats demonstrate that 4 days after parabiosis there is an appreciable quantitative increase in the formation of gamma globulin and depression of the albumin fraction (Kamrin and Murray) Both of these facets of information prompted the present experiment to determine the effect of donor kidney tissue homogenate on the survival of donor kidney tissue transplanted to separated parabionts

## MATERIALS AND METHODS

Of the 48 pairs of littermate albino rats placed in parabiosis by a modified Bunster and Meyer technique, only 14 pairs were found to be in successful parabiosis Successful parabiosis is suggestive that individual variation has been reduced to a minimum between the parabionts (Kamrin, '54) On the thirtieth day of such successful union, the parabionts were surgically separated but each pair maintained in the same environment The right parabiont of each pair served as the experimental animal for the homogenate intraperitoneal injections and the left parabiont served as the control Both animals received the donor grafts on their right kidneys which were prepared by excising a piece of tissue the size of the graft and discarding it

The separated parabiont pairs were divided into three groups Group 1 consisted of 5 pairs of parabionts and 5 non littermate donors Group 2 consisted of 4 pairs of parabionts and 4 non littermate donors Group 3 consisted of 5 pairs of parabionts and 5 non littermate donors The right kidney was removed from each donor when needed for the preparation of the homogenate The whole kidney was homogenized with 7 5 cc of normal physiological saline Upon obtaining a uniform homogenate after approximately 10 minutes of grinding, the first injection of homogenate was made intraperitoneally into the right experimental animal of one pair for which the donor was later to supply kidney tissue for grafting Immediately after the injection the rubber stoppered vial containing the homogenate was quick frozen It was rapidly thawed in warm water for subsequent injections and refrozen for storage

Group 1 Five injections of 0 5 cc on alternate days (right animals only) On the day of the last injection, the remaining left kidney of the donor was exposed and two slices of kidney tissue removed obliquely from the superior and inferior poles and placed on the prepared kidney sites of the right experimental parabiont and left control parabiont The grafts were held in place until adherent and the abdominal wounds closed

Group 2 Each right parabiont of the four pairs received 7 homogenate injections on alternate days Subsequent treatment of both parabionts of each pair was the same as above

Group 3 Each right parabiont received 10 homogenate injections on alternate days Subsequent treatment of both parabionts of each pair was the same as in group 1

All experimental and control parabiont pairs were maintained for 1 month following transplantation and then sacrificed The grafted kidneys from both animals were removed, fixed and later prepared for histological study

## RESULTS

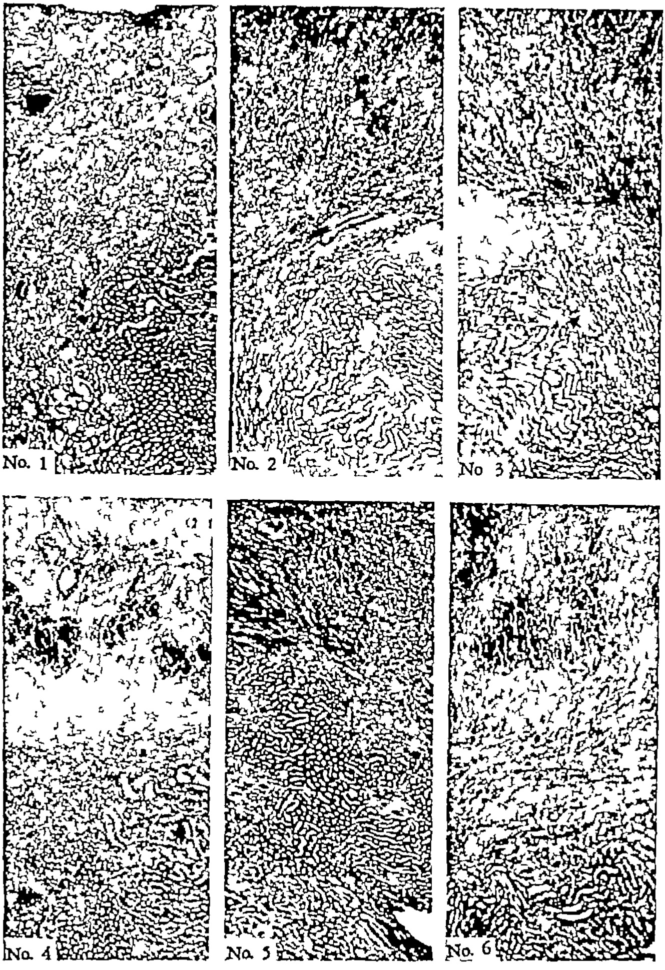
The *controls* for all the groups were the left co-parabiont of the pair in each group Each of these animals had been in parabiosis for at least one month and then had been separated for periods of 40 to 70 days prior to receiving the donor kidney tissue homograft on the prepared site on the right kidney None of these animals received a homogenate injection

In all controls, the grafted host kidney showed a mild to moderate reaction near the bed of the graft with the exception that a more severe reaction with the formation of a connective tissue barrier was evident where the graft abutted the host's collecting tubules In this area, there was an enormous increase in parallel running vascular channels plus the inclusion of blood within the collecting tubules themselves Many of these extra interlobular blood vessels penetrated through the graft bed and were found ascending into the graft Some of these capillaries were seen to anastomose with descending capillaries from the perirenal fascia so that a vast network of vascular channels was found within the graft

All the grafts placed on the kidneys of the control animals remained in place during the experiment Grossly, the area of graft placement was seen as a light yellowish raised patch on the host kidney Histologically, the grafts presented a demarcated phantom appearance similar to that found during the reciprocal exchange of kidney tissue between separated co-parabionts (Kamrin, '56) Perhaps, because the kidney tissue grafts were obtained from unrelated donors, these homografts demonstrated numerous connective tissue encapsulated necrotic areas In addition, an excellent blood supply was found running between these encapsulated areas with apparent extensive stromatization Figures 1, 2 and 3 clearly illustrates the appearance of the grafts and the interzonal area between the graft and host

The *experimental* animals which received 5, 7 or 10 intraperitoneal homogenate injections demonstrated a somewhat different response to donor kidney tissue homografting Group 1 which received 5 homogenate injections prior to homografting showed the following effects The host tissues adjacent to the graft bed showed a mild reaction with maximum infiltration of leukocytes in the collecting tubule area At the interzone between graft and host, the host's adjacent parenchymal tissues appeared functional and undisturbed Although numerous blood vessels from the host have grown into the graft, little connective tissue has formed In figure 4, areas of circumscribed degeneration are found as are also isolated areas of slowly degenerating parenchymal tissues in which cellular pyknosis is evident Some phantom representations of the glomeruli and tubules were found but they were not so evident or widespread as were found in the controls

Group 2 receiving 7 homogenate injections demonstrated somewhat lesser reaction in the host tissue adjacent to the interzone, but greater reaction within



Figs 1 2 3 Histological sections from three control animals illustrating retention of unrelated and non littermate albino rat kidney tissue homografts (above) on recipient host kidney (below) for 30 days ×55

Fig 4. (Animal K-8R Successful parabiosis for 34 days subsequent separation for 30 days ) Recipient received 5 donor homogenate injections intraperitoneally on alternate days Homografting of kidney tissue from donor made on last day of injection Duration of graft *in situ* prior to removal—30 days ×55

*Fig 5 (Animal K 10R Successful parabiosis for 30 days subsequent separation for 30 days )* Recipient received 7 homogenate injections prior to homografting Following procedures same as above ×55

Fig 6 (Animal K 7R Successful parabiosis for 35 days subsequent separation 30 days ) the graft There appeared to be greater vascularization and more numerous remnants of the degenerating parenchymal tissues distributed among numerous fibroblasts (fig 5) Encapsulation of discrete areas of degenerating parenchymal structures was not found as frequently as in group 1 experimental grafts

Of the five experimental grafted kidneys in group 3, three had developed cysts and two had localized necrotic areas distributed throughout the graft Between the necrotic areas of the latter, an extensive vascular network was found rivalling that of the other groups The host reaction and interzone area shown in figure 6 is particularly interesting in that definite signs are seen of the host's parenchymal structures encroaching on the graft Also of interest is the finding of partially degenerated graft parenchymal structures within the lumen of the cyst In many instances, cell outlines and nuclei can be distinguished No blood vessels were found penetrating into these detached pieces of homograft

## DISCUSSION

The experimental animals were subjected to two conditions prior to homografting First, they had been in successful parabiosis and had demonstrated their ability to tolerate their interchanged blood supply and tissue fluids and cells Second, they had been exposed to a complex of cells and fibers of the injected donor kidney for a sufficient time to build up antibodies Both of these factors must have taxed the recipient's reticulo-endothelial system to the utmost On the other hand, the controls had been subjected only to the earlier parabiotic union and had not been "immunized" to the donor homograft In both instances, experimental and control animals, the grafts were retained and not sloughed off as is the finding in kidney tissue homografting to single animals

The use of donor homogenized kidney tissue was predicated on the findings of immunologists who claim that one or more parenteral injections of foreign materials generally cause the appearance, within a few days, of substances (antibodies) which possess the unique property of reacting with material injected (Kabat and Meyer, Rowley) Further, that the best portal by which the material should be injected is through the intraperitoneal route (Rowley) Workers in the field (Pressman) have demonstrated that anti-kidney antibody principally localizes in the glomerular tufts Whether such antibodies are available to neutralize or react with the antigenic effect of the donor kidney tissues by reacting at the graft site or by fixing antigens in the host kidney is uncertain and not clearly defined in the literature The closest approach to the problem is the work of Molomut et al in which recipient mice were sensitized by repeated injections with crystalline antigen and then subjected to a final local injection to produce a localized inflammatory response The results obtained in the group receiving 10 homogenate injections, in which the host tissue appears to grow toward and into the degenerating graft would suggest that the host had been sensitized to the graft, but the final massive reaction occurred within the graft substance itself The response to five injections and the time involved (10 days) appear to indicate that the dosage was sufficient to prevent destruction of the graft but not enough to maintain its integrity On the other hand, 7 injections in 14 days appeared to stimulate vascularization and retention of phantom representations of the parenchyma However, it must be noted that at best, none of the experimental results are so good as those seen in the controls in which no homogenate was given

The constituents of the homogenate are of interest Fink et al and Kalis and co workers demonstrated that both lyphilized and fractionated homogenates had active potentialities in the enhancement of tumor growth The work of Dixon, Bale and Spar and Pressman on the immunologic effects of protein labeled substances would indicate that the viability of the injected substance plays no part in fostering antibody formation It was quite evident that aside from the initial injection of the freshly made homogenate, all subsequent injections of the frozen and thawed homogenate were of dead cells On this point it is noteworthy that Chase found that splenic cells which have been damaged by freezing fail to induce the anaphylactic state That the latter is not a criterion (Kabat and Benacerraf) in antibody formation or in stimulatory effects, one can cite the work of Breuhaus and McJunkin and Andres in which it was found that the injection of homogenized kidney tissue into adult and embryonic animals would result in an increased count of parenchymal mitosis and homologous growth effects

The present findings suggest that the process of homografting is one of immunological acceptance or rejection Only during the status of continuing successful parabiosis are there found the optimum conditions for the survival of the kidney tissue homograft Separating successful parabionts and interchanging kidney tissue homografts or using a non littermate's kidney tissue to the kidneys of these parabionts will result in a retained but degenerating graft Adding donor kidney homogenate to the separated parabiotic status appears to heighten the degeneration of the graft but minimizes the host reaction Peculiarly, the presence of a more than adequate blood supply in the graft demonstrates that the localized necrotic areas are not due to infarction but to probable localized "immunologic" reactions

## SUMMARY

Kidney tissue from unrelated albino rats can be homografted to the kidneys of albino rats which have been separated from the state of successful parabiosis These grafts will not be viable to the extent that their parenchymal structures will be functional but will be well stromatized and vascularized

The intraperitoneal injection of donor kidney tissue homogenate into the recipients of donor kidney homografts will result in greater reaction in the graft and lesser reaction in the host tissues

The presence of an adequate blood supply in the graft derived from both the host and perirenal fascia would indicate that the reaction of the graft in the homogenate injected animal was due to local interactions probably of an immunological nature

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# TECHNIQUE TO DETERMINE AT OPERATION AREA OF RENAL PARENCHYMA SUPPLIED BY AN ABERRANT VESSEL

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During the operation for the relief of ureteral obstruction caused by an aberrant vessel, it is important to determine the exact amount of kidney supplied by the anomolous artery prior to its section. If too large an area is served by the vessel it may be injudicious to ablate it and thus deprive the body of a large functioning volume of renal parenchyma. This is particularly so if the disease is bilateral or if the opposite kidney is in any way impaired. In addition, leaving a large portion of necrotic kidney behind leads to secondary infection both aerobic and anaerobic.

In those cases where the vessel is deemed important, a procedure which separates the ureteropelvic junction from the vessel is best accomplished. If necessary, section of the ureter at the ureteropelvic junction and reimplantation in another site in the pelvis may be the procedure of choice.

The time honored and standard method of determining the vascular bed of an aberrant artery has been to clamp the vessel with a rubber-shod clamp for a period of 10 minutes and observe the demarcation line between the ischemic area and the normal portion.

This has several disadvantages. First, if waiting 10 minutes can be avoided one should do so inasmuch as the patient is under anesthesia with an open wound. Second, in event the vessel is deemed essential, delayed thrombosis may result from the prolonged clamping and change the result of the procedure originally done. Third, the demarcation line in this method is not clean-cut and this vagueness leads to poor resection.

The author has been using a technique which obviates the foregoing objections. This is to inject 7½ cc indigo carmine into the vessel in question with a small hypodermic needle. This renders the renal parenchyma supplied by the artery a deep blue which lasts several minutes and gives a sharp line of demarcation deep into the cortex of the kidney. This allows accurate section of the kidney.

In instances where the aberrant vessel may be smaller than is deemed safe to inject (because of thrombosis from intimal damage) the main renal vessel is injected and the blue coloration then occurs in the portion not supplied by the anomolous vessel.

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# EXPERIMENTAL STUDIES ON THE RECONSTRUCTION OF THE NEUROGENIC BLADDER A PRELIMINARY REPORT

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Attention has been drawn to the complex problem of the neurogenic bladder by the increased incidence of spinal cord trauma in civilian and war casualties Improvement in the immediate care of the injuries has resulted in a greater initial salvage rate The increased population of patients with neurogenic bladders suggests a need for re-evaluating the fundamental aspects of this problem The physiology and pathology of the normal and neurogenic bladder have been studied However, the innervation of substitute bladders has escaped the attention of previous investigators Furthermore, the utilization of these substitute bladders has not been fully explored

The present communication undertakes to describe 1) gross and cystometric observations in normal and reconstructed canine bladders, 2) intravesical pressure changes with stimulation of the nervi erigentes and vagi in normal and reconstructed bladders, 3) observations in animals following pelvic neurectomy, and dorsal rhizotomy, and 4) results following reconstruction of these types of neurogenic bladders

## HISTORICAL REVIEW

A *Experimental studies* One of the first concerted approaches to the physiology of micturition and its relationship to the neurogenic bladder was made by Barrington[1-6] He described six separate reflexes The first two complete their reflex arc in the brain stem They are as follows with increasing volume of the contents, the bladder contracts, and as the fluid forces the sphincter and runs through the urethra strong detrusor contraction occurs Since the remaining four reflexes are found in the spinal animal, they can be said to have their neurons within the spinal cord They consist of a slight rise of vesical pressure following distension of the internal sphincter not sufficient to force the external sphincter, active relaxation of the urethra when it is passively distended, relaxation of the external sphincter whenever the bladder responds to distension by contraction of the detrusor muscle and relaxation of the plain muscle of the urethra by distension of the bladder after spinal transection

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*Note by editor* Doctor Shoemaker and Long's paper was awarded first prize in the essay competition sponsored annually by the American Urological Association's Committee on Scientific Research, Dr Miley B Wesson, chairman

Read at annual meeting, American Urological Association, Boston, Mass May 29, 1956

[1] Barrington F J F The nervous mechanism of micturition Quart J Exp Physiol, 8 33 1915

[2] Idem The effect of division of the hypogastric nerves on the frequency of micturition Quart J Exp Physiol 9 261, 1915

[3] Idem The relation of the hind brain to micturition Brain, 44 23, 1921

[4] Idem The central nervous control of micturition Brain, 51 209 1928

[5] Idem The component reflexes of micturition in the cat Brain, 54 177, 1931

[6] Idem The localization of the paths subserving micturition in the spinal cord of the cat Brain, 56 126 1933

Following extirpation of the cerebral motor cortices bilaterally, Langworthy and Hesser[7] found that the vesical capacity was markedly decreased The bladder lost its capacity to accommodate increased quantities of fluid at low pressures presumably due to loss of the inhibitory controls of these higher centers Although the former habits of micturition (such as urination in accustomed places) were lost, the animal assumed a characteristic posture with the beginning of flow of urine Furthermore, it was found that defecation occurred with urination Langworthy and Kolb[8] demonstrated that transection of the brain stem caudal to the acoustic colliculi resulted in a loss of vesical tonus and a loss of contractions sufficient to empty the bladder, i e , retention with overflow incontinence They concluded that the tone of the muscle in the bladder is controlled by mechanisms similar to those of striated muscle In confirming Barrington's work, these authors also believed that abdominal contractions have a part in reinforcing micturition but are not essential Dees and Langworthy[9] sectioned the posterior sacral roots in cats Following this procedure normal micturition no longer occurred, the bladder enlarged to several times its original capacity and overflow incontinence developed

Langworthy and Hesser[10] also studied the effect of sectioning the motor and sensory sacral roots They found that after a variable period of time decreased bladder capacity and periodic micturition occurred Previously Langworthy, Reeves and Tauber[11] observed the influence of parasympathetic and sympathetic nerve fibers Sectioning of the parasympathetic nerve fibers resulted in essentially the same type of vesical pathophysiology as did sectioning of the sensory and motor roots, by contrast the sympathetics were found to be in no way essential to normal micturition In 1941 Langworthy, Kolb, and Lewis[12] summarized their investigations and other related work in a classic study "The Physiology of Micturition "

In 1945 Jacobson[13] presented an elucidating study of the effects of peripheral nerve lesions and spinal cord lesions in dogs He detailed the physiology of the three types of neurogenic bladders Sympathectomy was found to have no effect in the normal or neurogenic bladder The autonomous bladder resulting from section of the pelvic nerves was found to be hypertrophied hypertonic, and to have a large quantity of residual urine Section of the sacral sensory roots produced an atonic, dilated, poorly functioning bladder with overflow incontinence Destruction of the cauda equina or sacral portion of the cord resulted in the same type of bladder as did pelvic neurectomy Following complete transection of the lumbar or sacral cord an automatic or reflex bladder developed, characterized by slight hypertrophy and intermittent partial emptying

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[12] Langworthy O R Kolb I C and Lewis, J G Physiology of Micturition Baltimore Williams and Wilkins 1940

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*B Clinical studies* Our present understanding of the anatomy of the autonomic nerve supply to the pelvic organs is based on the meticulous dissections of Latarjet and Bonnet[14] in 1913, and Hovelacque[15] in 1927 The parasympathetic fibers derived from the second, third, and possibly fourth sacral segments form the pelvic nerve (nervi erigentes) which leads to synoptic connections in the pelvic plexus and in the bladder wall The sympathetic fibers from the lower thoracic and upper lumbar segments of the cord form the preaortic and presacral plexuses The latter forms the hypogastric nerves which lead to the pelvic plexus

One of the earliest studies on the action of the urinary sphincters was done by Wesson, Macht, and Young[16] In 1920, they described depression of the internal sphincter and prostatic urethra by contraction of the levator prostatae and rectourethralis muscles, thereby straightening the curve of the prostatic urethra According to these investigators, the bladder neck was opened by relaxation of the tonic contraction of the internal and external sphincter and by contraction of the trigonal muscle

Classical experiments on the physiology of micturition in human beings were conducted by Denny-Brown and Robertson[17] in 1933 They found the reactionary contraction of distension of the bladder was controlled by an unconscious restraining effect at low volumes, but intruded upon the consciousness as the volume increased When the threshold was reached, sensations of bladder fullness were perceived Internal sphincter contractions and relaxations were found to be entirely secondary to activity of the detrusor muscle The external sphincter was found to open only after the internal sphincter and appeared not to be relaxed by voluntary effort

Denny-Brown[18] also studied 6 patients with cord lesions, three involved the cauda equina, and three involved the cord cephalad to the sacral region Although two of the patients with cauda equina lesions suffered automatic bladders, subsequent investigators[7] [19] have doubted the completeness of the lesions In the third patient an autonomous bladder developed In the 3 patients with supranuclear lesions, neurogenic bladders of the automatic reflex type developed

A most thorough study of sphincteric action in neurogenic bladders by Denny-Brown and Robertson[17] [18] enabled them to conclude that after cord lesions the "internal sphincter" or bladder neck reflects a degree of contraction reciprocal to that of the detrusor, i e , when the detrusor contracts the internal sphincter

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[14] Latarjet, A and Bonnet, P Le plexus hypogastrique chez l'homme Lyon chir , **9** 610, 1913

[15] Hovelacque, A Anatomie des Nerfs Craniens et Rachidiens et du Systeme Grand Sympathique chez l'Homme Paris Gaston Doin, 1927

[16] Wesson, M B , Macht, D I and Young, H Anatomical, embryological, and physiological studies of the trigone and neck of the bladder J Urol , **4** 279, 1920

[17] Denny Brown, D and Robertson, E G On the physiology of micturition Brain, **56** 149 1933

[18] Idem The state of the bladder and its sphincters in complete transverse lesions of the spinal cord and cauda equina Brain, **56** 397, 1933

[19] McLellen F C The Neurogenic Bladder Springfield Chas C Thomas, 1939

opens probably because of the arrangement of the muscle fibers They believed the internal sphincter was not under separate neural control The external sphincter was reflexly active where the sacral segments survived, this sphincter maintained a tonic contraction which was relaxed reflexly by a certain degree of active vesical contraction More recently, Talbot[20] has brought the problem up to date by summarizing the observed facts, and general laws of physiology together with his experience on a large series of paraplegic patients He has evolved a concept of the physiology of micturition providing a basis for reasonably accurate predictions which can be translated into a satisfactory system of clinical management

*C Treatment of neurogenic bladders* Treatment of the neurogenic bladder in the chronic stage has been divided into two schools of thought, the conservative and the surgical Surgical or active treatment has been advocated by Emmett,[21 5] Thompson,[26] and Nourse et al [27] who have reported good results by applying transurethral resections to neurogenic bladders with significant residual urine Munro,[28-31] Prather,[32 33] and others have championed the conservative method which consists primarily of tidal drainage and urinary tract antisepsis

Talbot[20 34 35] has outlined a concerted and extensive program for bladder retraining and rehabilitation which embodied 1) closure of all fistulas (accidental as well as suprapubic), 2) eradication of infection, 3) transurethral resection for demonstrable bladder neck obstruction and 4) development of adequate bladder capacity with minimal or negligible residual urine through a carefully controlled training period In this training period every effort was made to establish voluntary bladder control by conditioning Tidal drainage was instituted immediately after the trauma while the bladder was still in a state of spinal shock by adjustment of the syphon levels, the development of excessive degrees of hypertonicity was avoided or minimized By meticulous attention to these and other conditioning techniques the intermittent partial emptying of the automatic reflex bladder may be modified and reinforced Eventually, control of micturition is achieved by training the patient to void voluntarily, anticipating the involuntary reflex emptying of the bladder In a series of 100 consecutive unselected paraplegic and quadriplegic patients, most of whose lesions were complete, Talbot[35] reported satisfactory results with adequate bladder control in 78 per cent

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[20] Talbot H S A Clinical Approach to the Physiology of Micturition Third Annual V.A Paraplegia Conference Boston October 12-14 1954

[21] Emmett J L Urinary retention from imbalance of detrusor muscle and vesical neck, treatment by transurethral resection J Urol 43 692 1940

[22] Emmett J L and Beare J B Bladder difficulties in tabetic patients with special reference to treatment by transurethral resection J A.M A 117 1030 1941

[23] Emmett J L Transurethral resection in treatment of true and pseudo cord bladder J Urol 53 545 1945

[24] Emmett J L Albers D D and Anderson R E Statistical and analytical review of the final results of transurethral resection for cord bladder J Urol 43 692 1940

[25] Emmett, J L Neuromuscular Disease of the Urinary Tract In Urology edited by Meredith Campbell Philadelphia W B Saunders Co 1954 vol 2

[26] Thompson, G J Cord bladder Restoration of function by transurethral operation U S Naval Med Bull 45 207 1945

[27] Nourse M H and Bumpus H E Care of the paraplegic s urinary tract U S Naval Med Bull 46 1053 1946

[28] Munro, D The cord bladder J Urol 36 710 1936

[29] Idem The treatment of the urinary bladder in cases with injury to the spinal cord Am J Surg 38 120 1937

[30] Idem Tidal drainage New Eng J Med 229 6 1943

[31] Idem The rehabilitation of patients totally paralyzed below the waist Ibid 236 223 1947

[32] Prather C C Spinal cord injuries Care of the bladder J Urol 57 15 1947

[33] Idem Spinal cord injury Some urological aspects J Urol 66 347 1951

[34] Talbot H S Cystometry and the treatment of vesical dysfunction in paraplegia J Urol 59 1130 1948

[35] Talbot H S Fourth Annual V.A Paraplegia Conference New York October 19-21 1955

Several neurosurgical procedures have also been investigated Munro[36] has advocated anterior rhizotomy of the lower thoracic and lumbar nerves for spastic reflex contractions of the lower extremities and for reflex abdominal contractions thought to cause or contribute to vesical irritability (i e , spastic reflex bladder) Hoen[37] first proposed bilateral block or section of the third sacral root for selected cases of retention The value of this procedure was subsequently confirmed by Heimberger et al [38] Sheldon and Bors[39] studied the effect of subarachnoid injections of alcohol in patients with complete supranuclear lesions Bors[40] also used pudendal nerve sections in order to relax the spastic external sphincter He also suggested temporary nerve blocks and spinal anesthesia not only to predict results of the permanent procedure but also as a definite treatment It was the opinion of Bors that the residual urine decreases in proportion to bladder capacity with the acute conversion of a supranuclear lesion to an infranuclear lesion Furthermore he found that the bladder became more amenable to external pressure Emmett[25] concurred with Bors in stating that “ a nonreflex bladder usually is a more serviceable one and can be treated more successfully than the inefficient reflex bladder ”

As early as 1930 Learmonth[41] performed presacral neurectomies, Cheetham[42] has advocated this procedure Meirowsky et al [43] suggest anterior rhizotomy and neurectomy in selected cases, after preliminary sacral block or spinal anesthesia These authors report good results which they attribute to relaxation of the perineal muscles and lowering of the vesical neck

The vesical lesions resulting from spina bifida have been notoriously unresponsive to therapy Talbot feels that the conservative method should be instituted as early as possible Emmett[44] reported satisfactory results in only 20 per cent of these patients, following transurethral resections Young[45] has utilized the technique of retropubic wedge resection converting a Y incision into a V to decrease vesical neck obstruction After experimenting with various methods of colostomies, Gross, Holcomb, and Swan[46] concluded that the most efficacious approach was that of permanent suprapubic cystostomy

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[36] Munro, D Anterior rhizotomy for spastic paraplegia New Eng J Med , **233** 453, 1945

[37] Hoen, T I Discussion of the Urological Problem Conference on Spinal Cord Injuries, Army Service Forces, Second Service Command, October 20, 1945

[38] Heimburger, R F , Freeman, L W and Wilde, N J Sacral nerve innervation of the human bladder J Neurol Surg , **5** 154, 1948

[39] Sheldon, C H and Bors, E Subarachnoid alcohol block in paraplegia J Neurol Surg **5** 385, 1948

[40] Bors E , Comarr, A E and Moulton, S H The role of nerve blocks in the management of cord bladders J Urol , **63** 853, 1950

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[43] Meirowski, A J , Scheibert, C P and Rose, D K Indications for the neurosurgical establishment of bladder automaticity in paraplegia J Urol , **67** 192, 1952

[44] Emmett J L , Simon, H B and Mills, S D Neuromuscular disease of the urinary tract in infants and children Pediat Clin N Amer , **2** 803, 1955

### MATERIALS AND METHODS

*A Preparation of reconstructed bladders* A series of 20 animals was studied In 11 dogs subtotal bladder resection was carried out leaving only the trigone, and the bladder was reconstructed with reversed seromuscular grafts from the ileum by means of a previously described technique[47] Most if not all, of the effective expansile component of the reconstructed organ was composed of the substitute graft The nine remaining intact animals served as controls

The animals were anesthetized with sodium pentothal intravenously Catheterization was performed with a No 12 Foley in the females, or with a No 7 urethral catheter in the male dogs Cystometry was performed under very light anesthesia with a Lewis recording cystometer and with a water manometer In a few instances cystometry was performed without anesthesia for comparative purposes

*B Exposure and stimuli of nerves in normal and reconstructed bladders* The vagi were exposed through a midline cervical incision, isolated and stimulated with shield electrodes and an electrodyne stimulator using voltages ranging from 2 to 100 volts and a frequency of 100 stimuli per second

The abdomen was opened in the midline to observe the gross changes in the bladder on vagal stimulation A large self retaining retractor was used to negate the influence of the abdominal musculature on vesical pressure In a few animals the rectus muscle and sheath were severed from the pubic arch With these precautions it was felt that any changes in the intravesical pressure due to extraneous causes were effectively eliminated Cystometry was repeated following plane 2 (or surgical) anesthesia before and after the abdomen was opened and at the conclusion of the experiment The nervi erigentes were exposed at point of entry into the pelvic cavity and stimulated with an electrodyne stimulator

*C Preparation of neurogenic bladders* Three types of neurological lesions were performed on 13 dogs In a series of 9 animals the nervi erigentes were sectioned close to their origin from the spinal nerves Cystometric measurements and stimulation of the pelvic nerves were made before and after their sectioning Extradural sectioning of the sacral posterior roots was done in 3 dogs and section of the cauda equina was performed in 1 animal The animals with neurological lesions were followed postoperatively with cystometric studies At appropriate stages after the neurectomies rhizotomies, or cauda section reconstruction of the bladder was performed with reversed seromuscular grafts from the ileum[47]

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[45] Young B W The retropubic approach to vesical neck obstruction in children Surg, Gynec & Obst 96 150 1953

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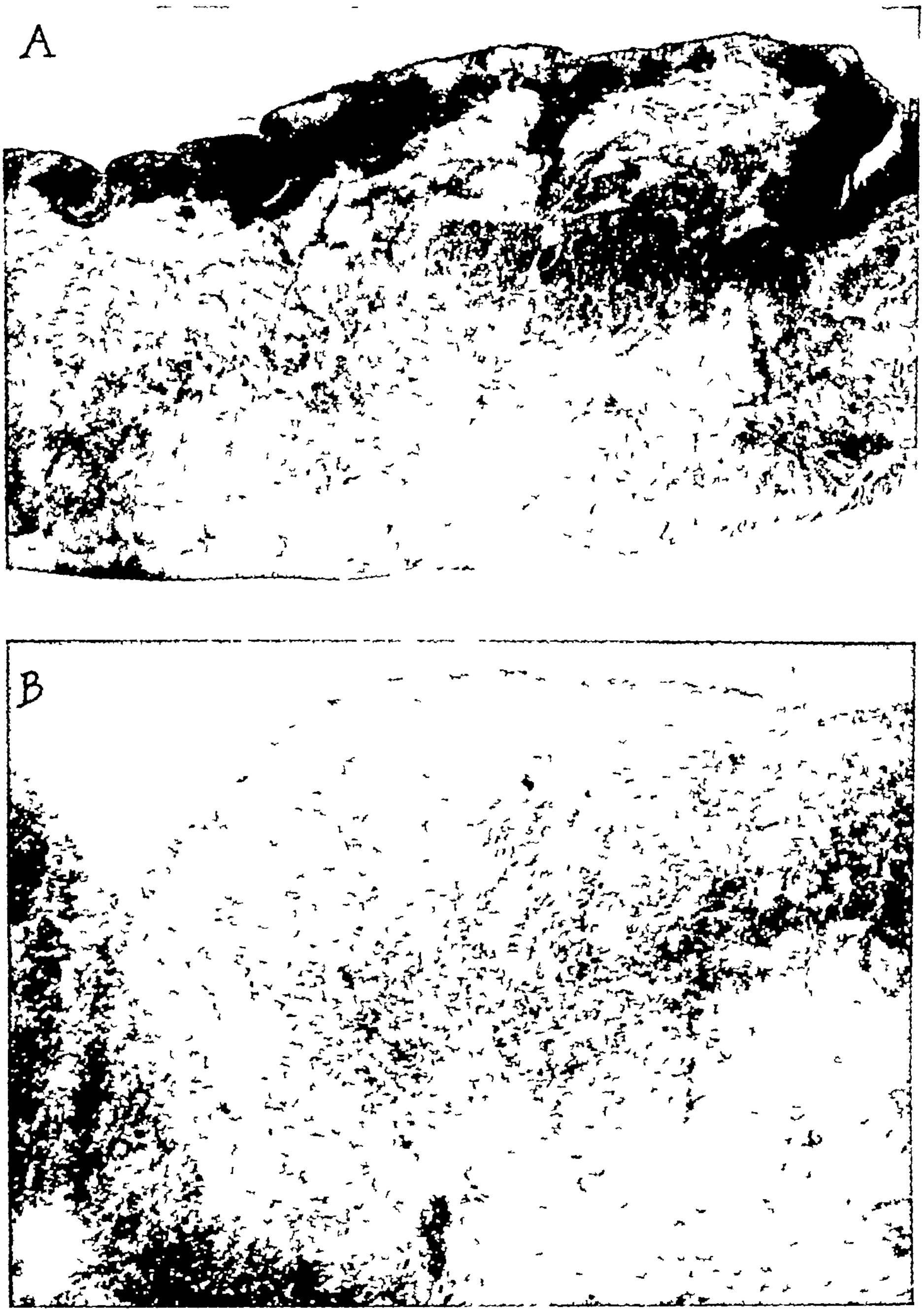

FIG 2 A, section of neurogenic bladder 20 days after pelvic neurectomy showing marked hypertrophy of bladder wall, cellular infiltration of mucosa and submucosa H & E stain X6 B high power view of previous section showing marked inflammatory reaction in sub epithelial layer Medium power H & E

*D Reconstruction of denervated bladders* Following denervation of the bladder, animals were observed for 1 to 4 weeks in order to demonstrate definite changes of severe functional impairment

Subtotal resection of the denervated bladder and reconstruction with ileal seg-

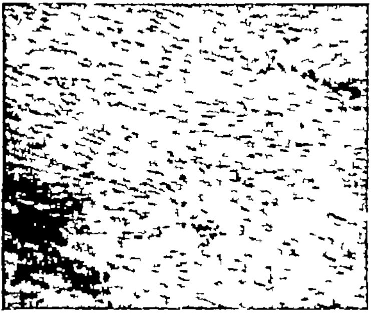

FIG 3 High power view of same section showing hypertrophy of detrusor muscle H & E

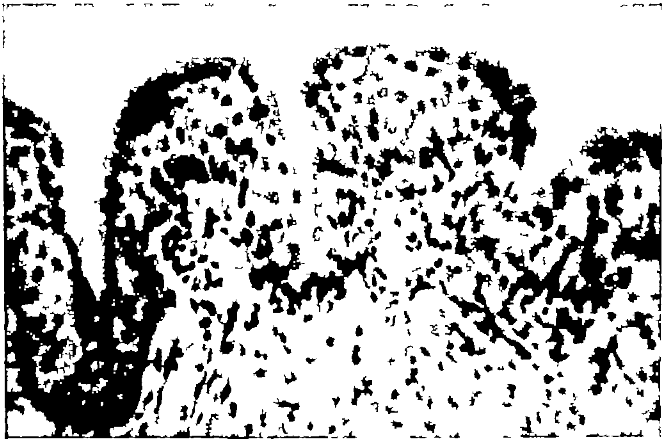

FIG 4 High power view of epithelial layer of reconstructed bladder showing transitional cell epithelium H & E

ments was performed and the animals were followed from 1 to 4 months Dribbling occurred shortly after removal of urethral and suprapubic tubes However, after the passage of a variable period of time continence developed Catheterization after voiding revealed no significant residual urine, a satisfactory capacity developed after 2 or 3 months

Two dogs whose bladders were reconstructed after pelvic neurectomy appeared to be continent only 2 weeks after reconstruction They voided 80 to 100 cc at a time with no dribbling between times Most animals however, require 1 or 2 months or more to develop capacity and satisfactory continence, depending upon the amount and severity of infection present In one of the dogs whose bladder was reconstructed the mesenteric pedicle to the bladder graft was severed, after

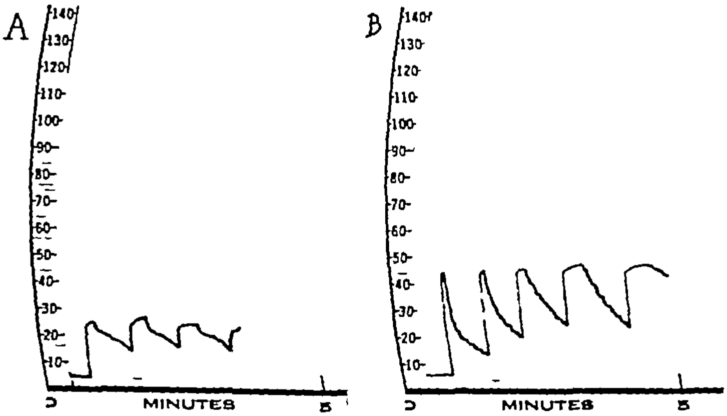

FIG 5 *A*, cystometrogram on dog No 1203 taken 8 days after pelvic neurectomy At that time, there was intermittent dribbling of small amounts of urine, residual and capacity of approximately 40 cc 12 5 cc increments *B*, cystometrogram taken 4 weeks after bladder reconstruction 25 cc increments Animal previously had been subjected to pelvic neurectomy Bladder capacity 120 cc

the dog was found to have a normal voiding pattern A neurogenic bladder promptly developed with a capacity of 35 cc, residual urine, incontinence, and hypertonic cystogram We excised this graft and reconstructed the bladder a second time The dog now has good control, no dribbling and has developed satisfactory capacity

## DISCUSSION

Although tremendous strides have been made in the management and care of the patient with neurogenic bladder in the past few decades, there still remains a significant number of patients in whom less than satisfactory results have been obtained In the present approach to this problem a review of the essential pathophysiology was made Clinical and experimental studies indicate that voluntary control of micturition and complete emptying of the bladder are mediated through several pathways The sacral parasympathetic outflow and accompanying sacral posterior root fibers constitute the peripheral component of the nervous pathway Long fiber tracts in the posterior columns and lateral columns of the spinal cord conduct nerve impulses to and from higher centers in the brain Interruption of the continuity of these pathways produces what has been termed the neurogenic bladder

In the neurogenic bladder urosepsis incident to urinary retention, inadequate bladder capacity, incontinence, and over-distention consequent to lack of voluntary control of micturition are problems which arise to plague the urologist

Reconstruction of the bladder with intestinal segments is not merely the replacing of the muscular wall of the excised organ, or the substitution of intestinal smooth muscle for bladder smooth muscle The intestinal graft has an intact mesenteric pedicle through which there is not only a vascular supply, but, more important, there are neural connections with the central nervous system

The intrinsic properties of the smooth muscle fibers of the grafted segment are not altered However, with the rearrangement of the gross structure and the relationship of muscle fascicles, peristaltic activity disappears The myotatic and myotonic reflexes which formerly gave rise to peristaltic activity become functional in a manner simulating the normal activity of the urinary bladder In addition, a neuronal communication between the reconstructed bladder and the central nervous system is provided by the afferent fibers of the vagus nerve In order to explain the results of these investigations, two important basic hypotheses must be considered, either or both of which may be operative The change in environment may evoke an alteration in the biochemical structure of the muscle cell resulting in a different response to the same nervous stimulus In addition there is the possibility that such a graft may result in re-establishing contact with the brain centers controlling voluntary micturition after spinal cord lesions

Evidence from these experiments suggests that functional restitution of the reconstructed bladder has indeed occurred Apparently the autonomic nerve supply of one organ may be substituted for the autonomic nerve supply of another, providing the receptor tissue is transplanted with it The concept that such a complex function as normal micturition could be accomplished through the transplanted vagal pathways was intriguing Such a phenomenon of transference of function in the central nervous system of mammals has not yet been described

Obviously these possibilities warrant further investigation and elucidation in the fundamental medical sciences as well as related clinical fields The truly voluntary activity of this type of graft, however, can be proven only by its application in the paraplegic patient

## SUMMARY AND CONCLUSIONS

The normal physiology of micturition and its relation to the neurogenic bladder were briefly reviewed A number of the present therapeutic approaches to this problem were outlined

Observations on the micturition pattern and cystometry on a series of dogs with bladders reconstructed from ileal segments were found to be essentially normal

Stimulation of the vagus nerve in the normal animal elicited no change in intravesical pressure Stimulation of the pelvic nerves produced a prompt visible contraction of the detrusor muscle with increase in the intravesical pressure

Stimulation of the vagus nerve in dogs with reconstructed ileal bladders was found to produce a pronounced rise in intravesical pressure

Stimulation of the pelvic nerves in dogs with reconstructed ileal bladders was found to have no demonstrable effect on the intravesical pressure indicating the absence of regeneration of the sacral parasympathetic fibers into the graft

The results of dogs subjected to posterior neurectomy and dorsal rhizotomy confirmed those previously reported in the literature

Neurogenic bladders induced by pelvic neurectomy and posterior rhizotomy were reconstructed with ileal segments Preliminary observations on these animals from one to three months revealed no significant residual urine after voiding adequate capacity, continence, and essentially normal cystometry

The possible significance of these experimental observations was discussed

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# SERTOLI CELL TUMOR IN AN INFANT

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Neoplasms of the infant testis are rare Between 1930 and 1950, of 113 consecutive cases of tumor of the testis seen at the University Hospitals only 3 occurred in the first decade of life Gilbert collected 5,500 patients with neoplasms of the testis from the literature, and within this group 131 were found in children under 15 years of age The largest collected series of testicular neoplasms occurring in children under 15 years of age was reported in 1925 by Julian, who analyzed 137 cases and found that the highest incidence occurred in the first 3 years of life Twelve cases under the age of 12 years were reported by Rusche and 4 of these were present in newborn infants Recently a newborn infant delivered in the University Hospitals was noted to have an enlarged, solid, testicular mass which proved to be a neoplasm This case is the subject of this report

## CASE REPORT

On September 19, 1955, a boy (B K M ) was born by a normal, spontaneous delivery His birth weight was 4,275 gm and the body measurements were normal Physical examination on admission to the newborn nursery was normal except for a hard, round, smooth, nontender mass in the right scrotum which replaced the testis This mass was 7 to 8 times the normal size of the infant testis The left testis was normal in size, shape and consistency

The mass did not transilluminate and an attempt at aspiration was performed without the recovery of fluid An inflammatory process or torsion seemed unlikely because the patient's temperature was normal and the mass was nontender The maternal serology was negative and no evidence of maternal tuberculosis was found Two possibilities remained that of hematocele or neoplasm and we were unable to satisfactorily differentiate between them

On September 21, 1955, a right orchiectomy was performed The mass in the right scrotum measured 2 8 by 2 by 1 1 cm and was nodular, although the tunica albuginea was intact (fig 1, *A*) On cut section the usual soft, brownish testicular tissue was replaced by a solid, firm, rubbery, golden-yellow, lobulated mass of tissue The lobules were separated by thin, greyish-white septa which imparted a gritty sensation when cut In the center of the mass there was an area of hemorrhage which presumably occurred when the attempt to aspirate the mass, the day prior to surgery, was made (fig 1, *B*) At the superior pole of the tumor near the cord was a portion of normal appearing testis measuring 5 mm in its greatest diameter The spermatic cord was normal

Multiple sections from tissue fixed in both 10 per cent formalin and Bouin's solution were stained with hematoxylin and eosin In addition, selected sections were stained by the allochrome and periodic acid-Schiff techniques Frozen sections of formalin fixed tissue were stained for lipids with Oil Red O

Histologically, there was a variable picture from one area of the tumor to

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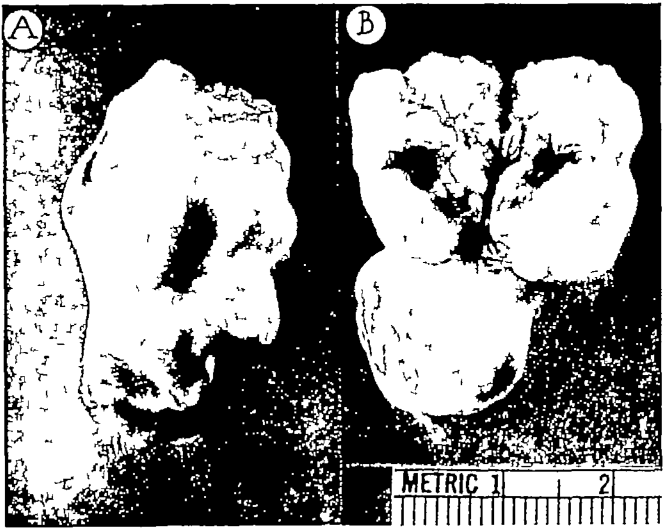

FIG 1 *A* gross appearance of neoplasm *B* cross section of neoplasm

another There was both a stromal and an epithelial component with an apparent transition between the two The stromal cells had oval to spindle shaped nuclei which showed a moderate variation in size and were surrounded by a poorly defined rim of cytoplasm The stroma tended to be loose and edematous in those areas where epithelial elements were least prominent (fig 2, *A*) and more dense where epithelial elements were more prominent (fig 2, *B*) A moderate amount of collagen was demonstrated by the allochrome stain Scattered through the stroma were cells with a round, relatively large nucleus surrounded by a well demarcated rim of finely vacuolated cytoplasm These cells were more numerous in the edematous portions of the stroma They contained fine lipid droplets in their cytoplasm The epithelial component was represented by tubules lined by cells with round hyperchromatic nuclei sourrounded by a thin rim of poorly defined cytoplasm (fig 3, *B*) There was little variation in the size of these cells Solid cords of similar cells were also present (figs 2 *B* and 3 *A*) The tubules were filled with a thin, stringy eosinophilic precipitate Lying free in the lumina were a few vacuolated cells similar to those described in the stroma In the edematous stroma there were also many cystic spaces which were filled with a homogeneous eosinophilic precipitate Some of these were lined by hyperchromatic cells which stood out from the lighter staining stromal cells to a moderate degree Others were lined by flattened cells which were in no way different from the stromal cells These cystic spaces were close to well defined tubules in many instances with a suggestive transition from one to the other Mitotic figures were seen in both the

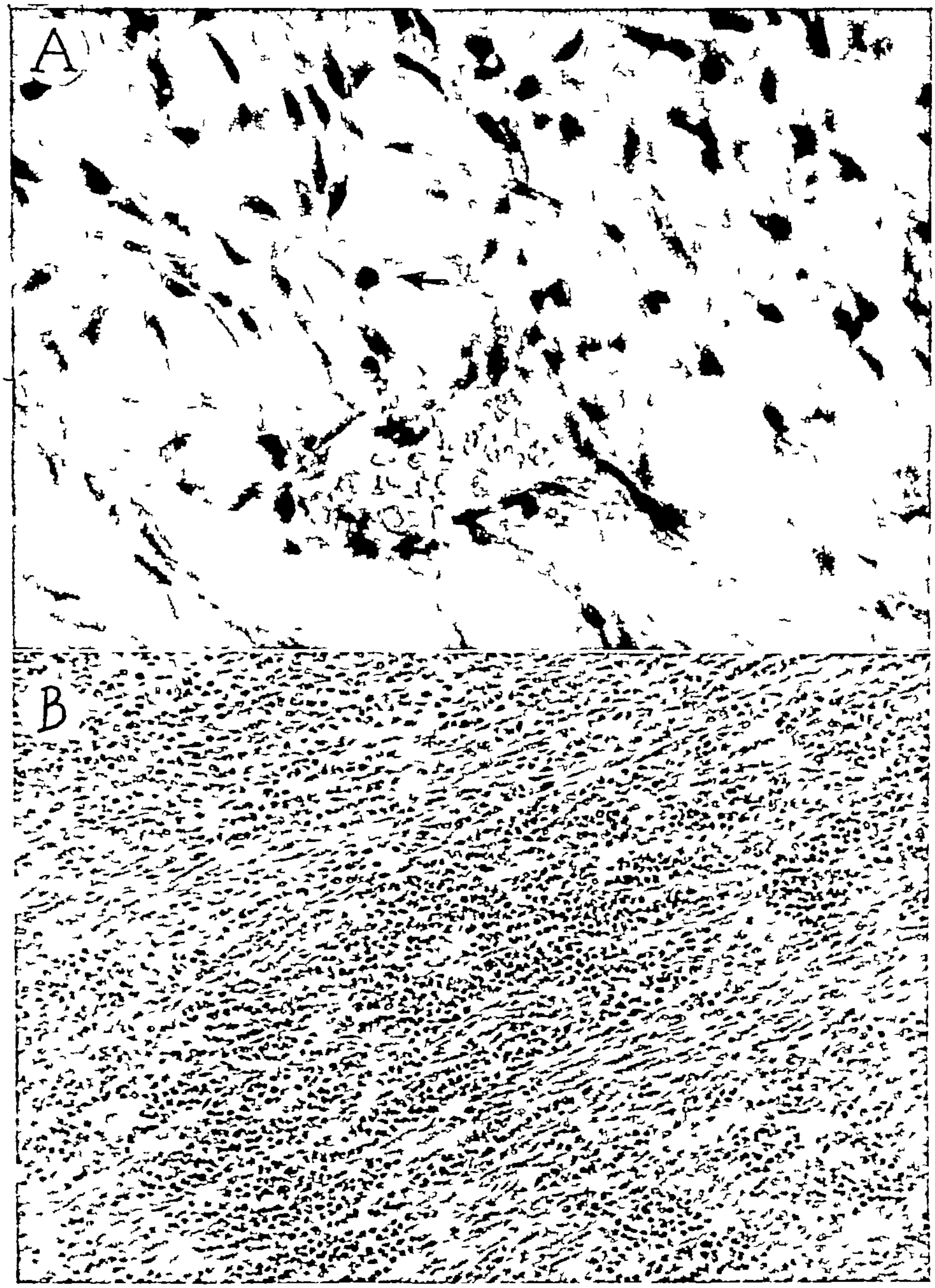

FIG 2 A, loose reticulated stroma containing cells with vacuolated cytoplasm which contained demonstrable lipid (arrow) *B*, cords and tubules of epithelial cells in dense collagenous stroma

stromal and epithelial cells There was a large area of hemorrhage in the center of one portion of the tumor with blood in the tubules and a hemorrhagic tract leading toward the tunica albuginea The tumor was incompletely separated into irregular sized areas by septa of less cellular fibrous tissue which faded imperceptibly into the tumor stroma There was a thin rim of normal appearing semi-

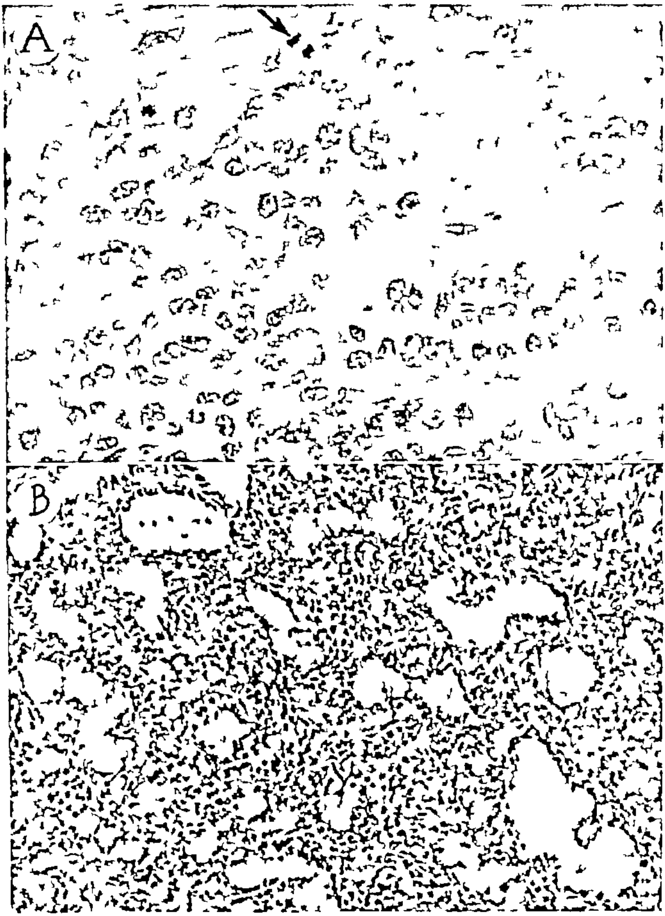

Fig 3 *A* high power of figure 1 *B* Note mitotic figure *B* tubular structures in a moderately dense collagenous stroma

niferous tubules along one border of the tumor separated from the tumor by a pseudocapsule similar to the septa just described An occasional seminiferous tubule was seen in this pseudocapsule and in the septa within the tumor A section from the grossly recognizable portion of testis near the spermatic cord revealed the tumor to be opposite a normal appearing portion of testis, separated from the rete testis by a thin band of fibrous tissue There was a definite resemblance between the epithelium of the tubules of the tumor and those of the rete testis The tunica albuginea was everywhere intact A section through the spermatic cord was not remarkable Sections stained by the periodic acid-Schiff technique showed nothing of note

Sections of the tissue were sent to Dr F K Mostofi at the Armed Institute of Pathology and it was his opinion that this was a "Sertoli cell tumor or androblastoma " Three additional cases have been registered with the Armed Forces Institute of Pathology and "all have behaved as benign tumors "

## DISCUSSION

Two aspects of this case were extremely interesting the age of the child and the classification of the neoplasm The majority of testicular neoplasms occur between the ages of 20 and 40 years However, approximately two to three per cent occur in the first decade of life Rusche records 4 cases in which a neoplasm was present at birth Matassarin, Meltzer and Bloom, Shane, Stevens and Rosenthal have recorded neoplasms in infants 8 months or younger To this we have added another infant whose neoplasm was present at birth and was removed 36 hours later So far as can be determined this is the earliest that any of these neoplasms have been removed The fact that these tumors have been found at birth and within the first 6 months of life serves to emphasize that they may have an embryonic origin

The vast majority of testicular neoplasms, 96 per cent, arise from the germinal epithelium While the same general types of neoplasms occur in infants and adults, it is interesting to note that practically all are mixed or teratomatous neoplasms, such as the embryonal cell carcinomas, teratomas or dermoid cysts Seminomas, the most common adult testicular neoplasm, are exceedingly rare in infancy A breakdown of 131 cases in children reported by Gilbert revealed that 42 were dermoid and 89 teratomas Rusche's 12 cases consisted of eight adult teratomas, three embryonal carcinomas and one dermoid cyst

The remaining 4 per cent of testicular neoplasms arise from other cellular elements in the testis or the supporting structures The most common type of neoplasm in this group is the interstitial cell tumor Other less commonly encountered neoplasms are fibromas, fibrosarcomas, hemangiomas, myomas, adenomatoid tumors and androblastomas or Sertoli cell tumors The androblastoma is thought to be the homologue of the ovarian arrhenoblastoma It was first recognized by Teilum who reported 3 cases The Armed Forces Institute studies report that it comprises 0 4 per cent of all testicular tumors In the adult it often produces feminizing characteristics such as gynecomastia, while in a child it may produce isosexual precocious puberty It has been difficult to reconcile the hormonal effects produced by this tumor but a correlation of the clinical course and the histological components of this tumor offers an explanation of this paradoxical hormonal response Histologically these neoplasms are composed of tubular or diffuse stroma or both The tubular elements are thought to arise from the precursors of the Sertoli cells which are potentially capable of producing estrogens while the stroma cells are related to the Leydig cells whose hormonal production is androgenic Therefore, the resulting clinical response depends upon which of the histological elements is predominant Of all the cases reported to date, none has been malignant

Histologically this case was a mixed type androblastoma with both stromal and tubular elements present The tubular epithelium resembled that of the rete testis There were only a few cells present in the tubules resembling Sertoli cells However, as Willis indicates, there should probably be no sharp distinction between Sertoli cell tumors and rete epithelial tumors since both arise from histogenetically allied nonspermatic epithelia The stroma of the tumor showed scattered cells with lipid droplets in their cytoplasm which may possibly represent interstitial cells The overall resemblance of this tumor to some arrhenoblastomas was well seen

We can add little to the theories of histogenesis suggested by others (Teilum, 1946, and Moore et al ) In our case the tumor appeared to arise in one portion of the testis and thus was not a neoplasm of the entire right testicular anlage The tumor was within the tunica albuginea with a thin rim of normal appearing seminiferous tubules compressed along one border and with a portion of normal testis at one pole, both separated from the tumor by a compression capsule

## SUMMARY

A case of testicular tumor in a newborn has been presented with removal of the tumor within 36 hours after birth The microscopic appearance of this neoplasm places it in the small group of testicular neoplasms that arise from the nongerminal cells In this case it was an androblastoma or Sertoli cell tumor

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# ON THE POTENTIAL ENZYMATIC CONTROL OF URIC ACID METABOLISM

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When it is necessary to remove excess uric acid from circulation as in the treatment of gout, kidney stones, or the metabolic disturbance caused in cancer therapy, it has been thought possible to apply the enzyme uricase In 1943 Oppenheimer and Kunkel demonstrated that intramuscular injections of a crude uricase preparation in "gouty" chickens readily effected reduction of elevated plasma uric acid levels and prevented an increase in plasma uric acid of normal chickens on a gout-producing diet [1] A less crude uricase preparation obtained in 1949 by Altman et al on repeated administration caused anaphylactoid reactions in fowl and in suitably sensitized rabbits [2] By using two-fifths of the quantity of uricase preparation less severe reactions developed in their rabbits They, too, succeeded in lowering the uric acid levels of the circulating systems of chickens, but pessimistically concluded that control of uric acid metabolism in man was unfeasible because of anaphylactoid reactions

We now report that more highly purified preparations obtained in this laboratory[3] also lowered plasma uric acid levels in chickens, and for the first time demonstrated that such a preparation would not induce anaphylactoid response in animals

## METHODS

*Sterility of preparations* Since the preparations studied cannot be made sterile by filtration or heat and remain active[3] the maintenance of low bacterial numbers was solved by keeping toluene in contact with the preparations At all stages, when the purification was not in progress a thin layer of toluene was placed over the preparation In preparing for animal use the following steps were taken Vials and their stoppers were sterilized To each vial, 0 1 ml of toluene was added, and this was followed by 10 ml samples of enzyme suspension The vials were then sealed using sterile techniques They were rapidly inverted 3 or 4 times to mix the aqueous and toluene phases This was repeated twice daily until sterility was assured The criterion for sterility was the absence of growth for 48 hours after inoculation in suitable aerobic and anaerobic media

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[2] Altman K I , Smull, K and Barron, E S G A new method for the preparation of uricase on the blood uric acid levels of the chicken Arch Biochem , **21** 158, 1949

[3] London M and Hudson, P B Purification and properties of solubilized uricase Biochim Biophys Acta (In press)

*Chicken studies* Birds, in general, excrete uric acid as the major end product of protein metabolism They therefore provide a means of testing preparations for *in vivo* uricolytic potentiality Ten normal, healthy, 7-month-old hens (Plymouth Barred Rocks), weighing 2 5–3 0 kg were fed a standard corn grain diet ("Ful O Pep Flock Ration," Quaker Oats Co ) and water *ad lib* Two ml samples of blood were drawn from either a wing or a femoral vein and placed in heparinized tubes to permit measurement of levels of uric acid Plasma uric acid levels were determined according to the method of Brown[4], after protein precipitation by the method of Folin and Wu[5] Chickens were divided into 3 groups, based on dietary variations arranged during the experimental periods Food was available at all times Group 1 Three hens fed only grain ration throughout, group 2 Three hens fed meat-grain mixture throughout group 3 Four hens fed grain ration except during periods of uricase injections, when meat grain mixture was substituted as the sole diet Blood samples were drawn at 2 week intervals in the pre uricase periods The following schedule of venipuncture was used during the uricase experiments A blood sample was taken prior to the injections of the enzyme Each hen was then given 0 7 ml of uricase suspension, intramuscularly The preparation administered contained 29 units per ml , and had a specific activity of $1.2 \left(\frac{\text{units}}{\mu\text{gN}}\right)^{*}$ Blood was drawn at 2 and 4-hour intervals after all uricase injections, from all groups Blood was drawn 17 hours later from each hen of groups 2 and 3

During the experimental period, all hens remained in good health The meat fed chickens almost doubled their original body weight within 4 months, whereas grain fed hens gained only about 25 per cent of their pre-experimental weights Deposition of fat in subcutaneous tissues of abdominal wall appeared to account for most of the weight increments of the meat-fed hens, since no fat was found in major internal organs No tophi or uric acid calculi were seen grossly or by repeated x ray examinations during the 4 month period of high protein diet

Table 1 demonstrates characteristic responses to intramuscular injections of uricase The response to uricase in chickens was most apparent after 2 hours and after 4 hours the effects of the uricase were almost gone Measurements of plasma uric acid made 17 hours after intramuscular administration of uricase provided values similar to the pre injection stage

Only about one half of the chickens manifested uricolytic responses to uricase This finding corroborates those of Oppenheimer and Kunkel[1] and Altman et al [2]

*Immunological and toxicological evaluation* Five female guinea pigs, each weighing about 700 gm , were given subcutaneously in the abdominal wall, 0 3 ml of the same uricase suspension administered to the chickens Eight days later, 2 of the animals were each given 0 5 ml of the same enzyme suspension in the same site Another guinea pig was given 0 5 ml of this suspension

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* A unit of activity is amount of enzyme required to break down 1 μg of uric acid/min at 37 at pH 9.2 and in solution where the concentration of uric acid is 5 μg /ml [2] The preparations used in this work were all at least 500 fold purified based on nitrogen values

[4] Brown H The determination of uric acid in human blood J Biol Chem 158 601 1945

[5] Folin O and Wu H A system of blood analysis J Biol Chem 38 81 1919

TABLE 1 *In vivo effects of uricase on plasma uric acid levels*

| Chicken No and Group | Level at Inj (mg %) | Level 2 Hrs Later | Level 4 Hrs Later | % Uric Acid Lowered in 2 Hrs |
|---|---|---|---|---|
| 486 II | 10 8* | 4 2 | | 61 0 |
| 451 III | 11 8† | 7 8 | | 34 0 |
| 497 II | 6 7 | 3 6 | | 46 0 |
| 403 III | 9 0 | 6 8 | | 24 0 |
| 467 III | 6 6 | 6 9 | | (−) 4 5 |
| 456 II | 3 4 | 3 3 | | 2 9 |
| 480 III | 5 8 | 5 4 | | 0 7 |
| Similar Experiment One Week Later | | | | |
| 486 II | 9 9 | 6 3 | 5 2 | 36 0 |
| 497 II | 4 4 | 5 1 | 5 4 | (−) 16 0 |
| 456 II | 6 8 | 6 3 | 7 6 | 7 4 |
| 480 III | 7 8 | 7 5 | 7 6 | 3 8 |
| 451 III | 11 2 | 5 9 | 6 8 | 47 0 |
| 459 I | 8 3* | 4 6 | 7 9 | 45 0 |
| 467 III | 6 3 | 7 0 | 8 0 | (−) 11 1 |
| 403 III | 7 1 | 7 6 | 8 5 | (−) 7 0 |
| 449 I | 4 3 | 3 7 | 4 8 | 14 0 |
| 490 I | 5 0 | 2 4 | — | 52 0 |

* In general, chickens maintained on a meat grain ration for 4 mos had plasma uric acid levels 30–50% higher than birds on a grain diet However, individual variations occurred (e g compare Nos 497 and 459)

† Equally elevated plasma uric acid levels developed within 24 hrs after ingestion of the meat-grain mixture, but persistent elevation did not result unless this high protein diet was continued

12 days after the initial dose The fourth and fifth guinea pigs were given 1 0 ml and 0 5 ml of the suspension respectively, 19 days after the initial dose The latter 3 doses were administered intraperitoneally Each guinea pig was given another 1 ml of the suspension intramuscularly 34 days after the initial dose Three female rabbits, each weighing about 2 4 kg were given 0 5 ml/kg body weight of the enzyme suspension intramuscularly Each rabbit was injected with 2 ml of the suspension 17 days later, at which time 2 animals received the dose intravenously and the third, intraperitoneally

No untoward reactions occurred in any of the animals, the anaphylactoid responses described by Boyd[6] were entirely absent None of the animals had any sign of infection during observation for one week after the inoculations

To obtain tests for toxicity and immunological reactions (anaphylaxis) that were more objective, and as a check on the validity of our results, a batch of purified enzyme was sent to another laboratory * The preparation contained 41 units per ml and had a specific activity of 0 60 $\left(\frac{\text{units}}{\mu\text{gN}}\right)$ The following is their report 'A Acute toxicity Ten or more mice received up to 1 cc of the uricase solution intravenously This corresponds to 30–50 cc/kilo No toxic effects were observed B Chronic toxicity Fifteen mice were divided into 3 groups of 5 Group 1 received up to 1 cc uricase solution/kilo by intraperitoneal injection, daily for 30 days Group 2 received 1 cc of a saline suspension of the solvent hydrocarbon alone intraperitoneally, daily for 30 days Group 3 acted as control

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[6] Boyd, W C Fundamentals of Immunology Interscience Publishers, 1947, p 314

* The Department of Clinical Investigation of the Warner-Chilcott Laboratories did the testing the results of which are reported here This preparation has been set as a standard having the lowest purity limit for further animal and human studies

"No abnormality of erythrocyte count, leukocyte count, hemoglobin concentration or color index was noted No abnormality particularly of livers was found on gross pathological examination of the sacrificed animals

"Twelve guinea pigs were primed with 3 injections of 0 2 cc uricase intraperitoneally (January 17, 19, 21) All twelve pigs were challenged 21 days later (February 11) by 0 2 cc uricase intravenously

"No toxic signs, anaphylactic or otherwise, were manifested by any of the twelve animals following the challenging dose "

*Serum studies* As a means of evaluating *in vivo* uricolytic activity it is for several reasons not sufficient to measure the breakdown of uric acid alone The rate of input of uric acid into the bloodstream is variable depending on endogenous nucleic acid breakdown and exogenous purine metabolism There are also indications of secondary paths of uric acid destruction other than by uricase The rate of urinary excretion is also variable In addition, man and birds will deposit uric acid, and these reserves may tend to maintain a constant level of uric acid in blood Klemperer[7] and Praetorius[8] among others, have shown that the end products of uric acid decomposition as catalyzed by uricase can be variable depending on environmental factors such as pH and the nature of the buffer ions present Environmental factors were of primary importance in determining the amount of allantoin produced

If in human blood the conditions are sufficiently constant among individuals so that the ratio of allantoin produced to uric acid destroyed is constant, it may be possible to evaluate the *in vivo* uricolytic activity To determine whether or not this is true citrated blood samples were obtained from 4 normal males Ten ml samples were incubated for 45 minutes in closed vessels* at 37°C after 0 1 ml of purified uricase was added This was much longer than was necessary to complete the reaction The samples were then placed in viscose membranes and exhaustively dialyzed against repeated changes of 0 9 per cent saline The saline solutions after dialysis were assayed for uric acid[4] and allantoin, according to the method of Young and Conway [9] Controls were similarly treated and analyzed, but no uricase was added Table 2 contains a summary indicating the variability of allantoin production The second and fourth columns serve as controls to show that dialysis was complete since the levels of uric acid and allantoin are approximately those expected

As has been observed on two previous occasions[1 2] and in a previous section

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[7] Klemperer F W Enzymic oxidation of uric acid J Biol Chem 160 111 1945

[8] Praetorius, E The enzymic conversion of uric acid spectrophotometric analysis Biochim Biophys Acta 2 602 1948

[9] Young E G and Conway C F On the estimation of allantoin by the Rimini Schryver reaction J Biol Chem 142 839 1942

* These vessels were closed to prevent the escape of $CO_2$ and thus to maintain the reaction at pH 7 4 In no case could there be a lack of $O_2$ since less than 5 per cent of the $O_2$ in the reaction vessel was used up in any of the curves plotted

TABLE 2. *Conversion of uric acid to allantoin in whole blood of 4 patients**

| mg % Uric Acid | Allantoin Formed (Mole Fraction) | mg % Allantoin (Before Uricase) |
|---|---|---|
| 2.36 | 0.56 | 0.86 |
| 2.26 | 1.02 | 0.88 |
| 2.19 | 1.09 | 1.12 |
| 1.76 | 0.24 | 0.90 |

* All values shown are calculated for whole blood, and are derived from dialysate analyses. Allantoin formed was obtained by subtracting control value from uricase treated fraction.

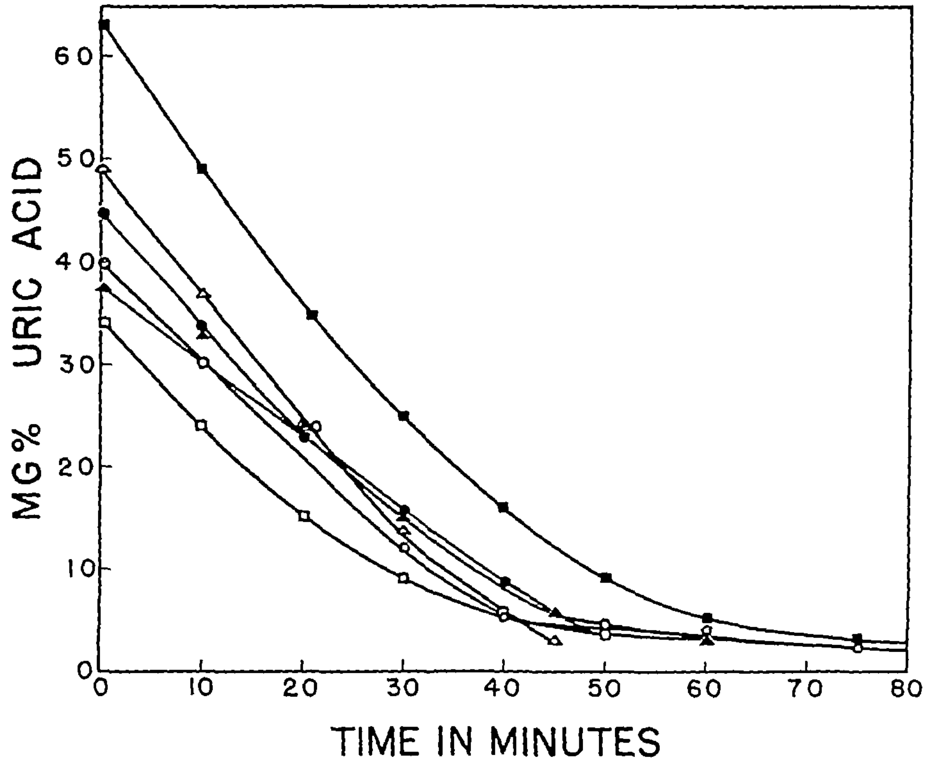

FIG. 1. Samples of sera drawn from human males were incubated at 37°C for 0.5 hr in open vessels to drive off CO$_2$. These were adjusted to pH 7.4 with NaH$_2$PO$_4$. 6 ml portions of each sample were treated with 0.1 ml of enzyme suspension, and then incubated at 37°. Half ml aliquots withdrawn at intervals were immediately precipitated in acid tungstate and assayed for uric acid according to Brown's method.

of this work, about one-half of the chickens given uricase preparations did not respond with lowered uric acid levels. If these circumstances prevail in humans then evaluation of the *in vivo* uricase activity may be further complicated. In figure 1 is a demonstration that sera alone vary sufficiently so that the rates of uric acid destruction in them are not equal. A 2-fold variation in rate was found among the six sera tested when the same preparation was used.

## DISCUSSION

In addition to the variants just cited, it is significant to note differences in oxygen tension of the serum of normal persons under like conditions. It is known that oxygen tension exerts an influence on the rate of enzyme reaction At least one other factor governs the rate of uric acid destruction this factor is intrinsic and appears to be peculiar to the given serum sample All these influences, in combination with the variability of the end products, as well as unknown data regarding input and storage of uric acid, serve to make difficult the evaluation of the enzyme in human beings Moreover, it appears that measurements of urinary output of allantoin and the decrease of serum uric acid are necessary in order to obtain even an approximate evaluation of the effectiveness of the enzyme in the human

Emphasis is placed upon the absence of anaphylactic reaction in the guinea pigs and rabbits given injections of purified uricase suspension at intervals Since the doses contained beef protein, sensitization of the animals could have been expected The failure of anaphylactoid response indicates that preparations have been obtained that may be used to control serum uric acid levels The evidence is most striking because the dosage of uricase designed to test sensitization in guinea pigs was almost thrice greater in proportion to body weight than that given to the chickens, and at least thrice greater in the rabbit The tests performed for the present preparation by Warner Chilcott provide a greater assurance of the safety of the purified material, especially because the preparation they used was half as pure as those used with animals in these laboratories

It is noteworthy that none of the chickens given multiple intramuscular injections of uricase showed any signs of anaphylaxis In each uricase injection *the chickens received about 100 µg of protein, as contrasted with several mg of* protein given by Altman et al in order to accomplish reduction of plasma uric acid of comparable degree This large difference in level of injected protein could be expected to make the difference between the observed results The potential usefulness of a preparation that destroys uric acid *in vivo*, with no side effects in animals, in the treatment of gout or kidney stones is apparent

Preliminary studies on the effect of the administration of uricase preparation in man have been begun in this hospital Further detail will be forthcoming in a later publication

## SUMMARY

It has been demonstrated that preparations of uricase free of anaphylactoid responses may be used to destroy serum uric acid in the chicken Immunological and toxicological studies on guinea pigs, rabbits and mice suggest that such a preparation may be safe for human use

There is considerable variation in the plasma of individuals, as tested *in vitro*, such that the quantity of allantoin produced would not be a good criterion of uricase activity *in vivo* On the other hand, there is evidence that the decrease of uric acid would also be a poor criterion of the *in vivo* activity of uricase

We wish to thank the Warner Chilcott Laboratories for donating their services, and Mr Armin Sommer for his skilful technical assistance in helping to complete this work

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# ANORCHISM WITHOUT EUNUCHISM

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Congenital bilateral absence of the testes has been thought to be synonymous with eunuchism, because by definition, eunuchism is the condition of a man or boy deprived of the testicles, with a loss of sexual power The purpose of this paper is to present a case in which eunuchism did not accompany anorchism, and to point out the explanation for this phenomenon which has been observed in only one out of the 14 cases of bilateral anorchism previously reported in the world literature

The first and only such case reported, and there are only sparse references to it, was in 1564 when Cabrol performed an autopsy on a man who had been hanged for rape, and was unable to find any testes[1] [2] [3] Since this fellow was punished for the deed we will give him the benefit of the doubt and assume he was guilty of the crime It would seem then that here is a case reported of a man without testes who presumably had normal sexual desires but lacked the necessary inhibitions to curb his passions

There has been a lapse of more than four centuries since the hanging and to date, no other case of a man with normal sexual desires and capable of ejaculation, but born with a congenital bilateral absence of testes, has been reported The second, and only documented case, of anorchism without eunuchism is reported below

## CASE REPORT

Hosp No 22331, D B C , a 19-year old, single, white man, a jet engine mechanic, was referred to this hospital on November 12, 1955 for the treatment of bilateral cryptorchism The history obtained from the patient is that he did not remember ever having testes in the scrotum He was seen by several doctors throughout childhood who recommended waiting until he was 17 or 18 before doing anything about it He was referred to a medical center for endocrine studies in July 1954, and a diagnosis of hypogenitalism due to primary testicular failure was made A course of depo-testosterone therapy was recommended but the patient entered military service before it could be instituted

His history reveals that he had a normal childhood along masculine lines He had the usual childhood diseases and never had undergone surgery He had mumps parotitis at the age of 17, but was not seriously sick As for his sexual development, masturbation commenced at age 13 He started dating girls at age 15, and although he had had no sexual relations, he had engaged in genital fondling and petting to the point of orgasm He regarded his general health as

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[1] Cabrol B Quoted by Koopman and Wildbolz

[2] Koopman, J Anorchia congenita Genesk gids, 8 309–320, 1930

[3] Wildbolz, Hans Ein Fall von Kongenitaler Anorchie Cor Bl f schweiz Aerzte , 47 1307–1314, 1917

good He thought that his height had increased 3 inches in the last 3 years Genital hair had appeared at age 16, and axillary hair shortly thereafter There was no chest hair He never shaved until he entered service, and since then he has shaved once a month His voice had always been high pitched, and he sang alto in the school chorus He lived in the rural South until entering service in January 1955, after graduating from high school He enlisted in the Air Force and apparently no note was made about his condition at the induction examination Doctors at the base where he took his basic training examined him and told him that he should not be in the Air Force, although no action was taken to bring about his discharge He next received training as a jet engine mechanic and thence was assigned to an Arctic base in October 1955

Review of systems was essentially negative Review of the endocrine system by symptoms was essentially negative except for the foregoing reference to testicular function

Examination revealed a rather tall, obviously hypogonadal male, with a high pitched voice, height 71 50 inches, stripped weight 141 pounds, pulse 72, blood pressure 118/70, scalp hair was normal There was no significant body hair except scant axillary and genital hair with a gynecoid escutcheon There was no gynecomastia The skin was moist and there was no acne His general examination was essentially negative except for the hypogonadal aspects Fat padding was not unusual There was good muscle volume and tone Examination *of the genitalia revealed the penis to be rather small and uncircumcised* being 2 inches long and 2¼ inches in circumference in the flaccid state There was a small amount of pigmented genital hair which was chiefly peripenile in location The scrotum was present but not developed, and gave no evidence of ever having been filled There was complete union of the scrotum at the midline raphe There was no evidence of testes in the scrotal inguinal, thigh or perineal regions Abdominal examination was negative Rectal examination revealed the prostate to be small firm, and symmetrically developed, and the seminal vesicles were not palpable

It was our impression on admission that the patient had bilateral abdominal cryptorchism with retarded development of the secondary sexual characteristics probably due to a primary testicular inadequacy (hypogonadism) or pseudohermaphroditism

Excretory urography revealed normal upper urinary tracts bilaterally and no evidence of adrenal enlargement Three 24-hour urine specimens were sent to the First Army Laboratory for 17 ketosteroid levels The results of the first were 17 mg /liter and 24-hour excretion of 22 mg The second specimen gave 18 mg /liter and 24 hour excretion of 21 mg The third specimen was lost in transit A semen examination was performed on a specimen collected by masturbation and it was moderately viscous with a volume of 1 5 ml No spermatozoa were seen X ray of the skull showed no abnormalities of the sella turcica

Operation was performed on December 12, 1955 under general anesthesia By three separate incisions, bilateral inguinal exploration and an exploratory laparotomy were accomplished The postoperative diagnosis was bilateral

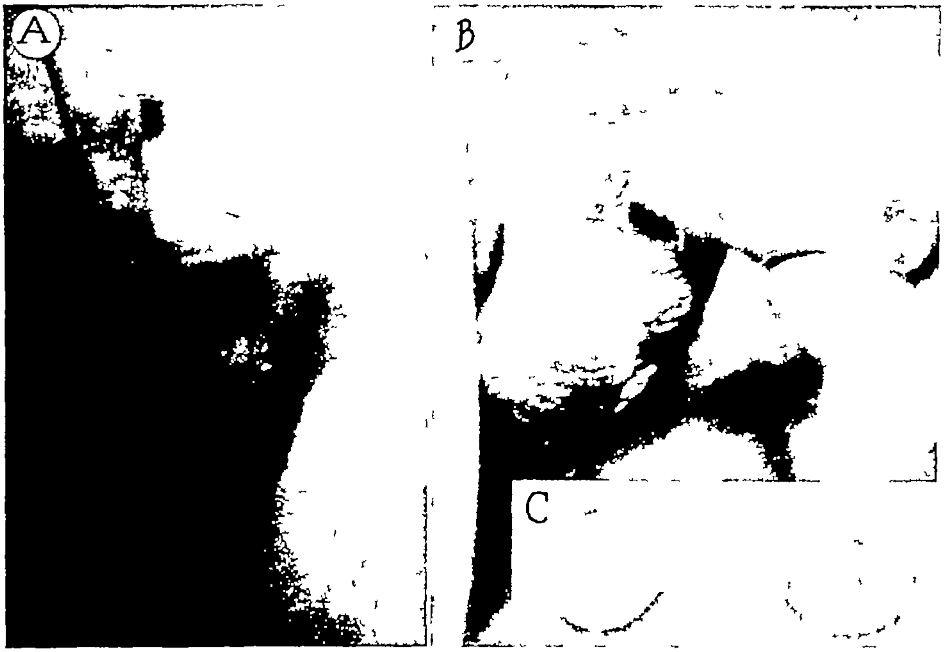

FIG 1 *A*, preoperative view of empty scrotum *B*, postoperative view showing testicular prostheses in place *C*, acrylic prostheses which were placed in scrotum for cosmetic effect Plastic testes manufactured in hospital's dental laboratory

anorchism At the operation, acrylic testicular prostheses were inserted into each scrotal cavity for their cosmetic effect See figure 1 (This had been discussed with the patient prior to surgery ) The operative findings were as follows On the left side the inguinal canal contained the vas deferens which entered the canal at the internal inguinal ring and egressed at the external ring to terminate at the neck of the scrotum as a fibrous band There was no evidence of an epididymis or a testis on this side On the right side, the inguinal canal contained a vas deferens which entered at the internal inguinal ring and made exit from the inguinal canal at the external inguinal ring It continued into the right scrotum where it terminated in a somewhat dilated structure which grossly resembled an epididymis and was attached to the dependent portion of the inside of the scrotum There was no evidence of a testicle on this side The findings on exploratory laparotomy, with both intraperitoneal and retroperitoneal inspection, revealed no remarkable structures No uterus, ovaries or testes were noted The patient was up and walking about on his first postoperative day and his postoperative course was completely uncomplicated and unremarkable

The pathology report (Clarence H Denser, Jr , Capt , USAF, MC, pathologist, Sampson AFB Laboratory Service), is as follows "The gross material arrives in two separate containers In one container, labeled 'left,' there is a long, tubular piece of tissue which measures 11 cm in length It has a diameter of approximately 1 0 cm which, in places, narrows down to 0 5 cm This structure is covered by smooth tissue, apparently representing peritoneal covering. This structure is sectioned serially at approximately 0.5 cm. intervals. The cut surface shows a mass of small tubular structures held together by loose connective tissue. The overall picture appears to be that of spermatic cord. There is no identifiable testicular tissue at either end of this structure. Several representative sections are embedded. On microscopic examination there is identified vas deferens, blood vessels, nerves, and islands of interstitial cells. No epididymal or seminiferous tubular tissue is identified.

"In a second container, labeled 'right,' there are three pieces of tissue. The first is a solid piece of tissue surrounded by bits of fibrous tissue and fat, which measures 2.0 by 1.5 by 0.5 cm. This specimen is sectioned and the cut surface shows a rather pale, homogeneous, rubbery yellowish tissue. A section is embedded. The other two pieces of tissue are tubular structures which measure approximately 6.0 cm. in length each, and have a diameter of 0.25 cm. Representative sections are taken from each of these structures and embedded for histological study. On microscopic examination of the sections of this right spermatic cord there is identified vas deferens, epididymis, blood vessels, nerves, *striated muscle, and islands of interstitial cells (Leydig cells). No seminiferous* tubular tissue or remains thereof is found."

The patient is pleased and comfortable with his scrotal testicular prostheses. His wounds healed well. At his own request, he was processed for discharge from service under the provisions of AFM 35-4 for a disability which existed prior to his entry into service. He realizes now that he is sterile but he states that he hopes to marry his girl friend back home and settle down as a farmer in the near future.

## DISCUSSION

The surgical treatment of cryptorchism has led to the reporting of an increasing number of cases of congenital absence of one or even both testes. Most recently, Counseller and Walker reviewed the literature in 1932[4] and counted 9 cases of bilateral anorchism from the Dutch and German writings, but were unable to find any reports in journals in the English language. They added 2 cases from their experiences at the Mayo Clinic. Heller et al., in a discussion of the endocrinologic changes in the prepuberal castration of males,[5] added two more cases of proved congenital bilateral anorchism. Hepburn,[6] in contributing his case and adding up the total somehow failed to take cognizance of the case reported by Le Gendre and Bastien in 1849[7] and came up with a total of 13 *instead of what properly should have been 14.* In none of these cases except the first, who hanged for rape, was there any evidence of the development of male sexual urges.

[4] Counseller, V. S. and Walker, M. A. Congenital absence of testes. Ann. Surg., 98: 104–109, 1933.
[5] Heller, C. G., Nelson, W. O. and Roth, A. A. Functional prepuberal castration in males. J. Clin. Endocrinol., 3: 573–588, 1943.
[6] Hepburn, R. H. Anorchism. J. Urol., 62: 65–68, 1949.
[7] Le Gendre and Bastien. Quoted by Koopman and Wildbolz.

The explanation of the normal sexual urges in the case herein reported lies in the finding of islands of interstitial (Leydig) cells located along the wolffian duct structures in both inguinal canals Extratesticular interstitial cells may occasionally be found in normal individuals[8] [9] [10] and are usually located in the male around the body and tail of the epididymis It is conjectured that these extratesticular interstitial cells found by the pathologist were responsible for the secretion of androgens which compensated somewhat for the absence of both his testes Since these cells have now been removed, it is believed that this patient will benefit from substitutional therapy in the form of depo-testosterone

The presence of mesonephric wolffian duct structures (vas and epididymis) in the absence of testes is not at all unusual This has been the finding in all of the cases of anorchism which have been reported, and may be explained embryologically[11] by their differences in origin, which will not be discussed in detail here

In the problem of differential diagnosis between abdominal cryptorchism and anorchism in the adult, it may be stated that in the former, although spermatogenesis is absent, the secondary male sexual characteristics develop normally, because the higher intra-abdominal temperature does not have the same adverse effect on the interstitial cells that it has on the germinal cells If a young boy however, does not have palpable testes, no attempt should be made to distinguish abdominal cryptorchism from anorchism because of the importance of surgically placing the testes in the scrotum long before puberty so that the spermatogenic function of the testes will not be irrevocably damaged The diagnosis of true anorchism can only be established by careful inguinal and abdominal intraperitoneal and retroperitoneal exploration

## SUMMARY

A case of congenital bilateral anorchism in a 19-year old man is presented and discussed His psychosexual development along masculine lines, with normal male sexual urges and the preserved ability to have ejaculations is attributable to the occurrence of extratesticular interstitial (Leydig) cells found scattered in islands along the wolffian duct structures in his inguinal canals

I should like to note my appreciation to Mary E Grinnel and Jane M Fulcher of the Armed Forces Medical Library, Washington, D C , for their making available to me photostatic copies of the quoted references

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[8] Tedeschi, C G and Burke, F E Paratesticular interstitial-cell tumor Cancer, **4** 312–318, 1951

[9] Altmann, F Uber Eunuchoidismus Virchows Arch f path Anat , **276** 455–547, 1930

[10] Masson, P and Sencert, L Cancer des cellules interstitielles Bull Assoc franc p l'étude du cancer, **12** 555–572, 1923

[11] Arey, L B Developmental Anatomy, 5th ed Philadelphia W B Saunders Co , 1946, pp 268–294

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# THE PROGNOSTIC SIGNIFICANCE OF AN ELEVATED SERUM ACID PHOSPHATASE LEVEL IN ADVANCED PROSTATIC CARCINOMA

EMIL J GANEM

*From the Urological Service of the Massachusetts General Hospital Boston Mass*

In a recent clinical investigation of patients harboring advanced prostatic carcinoma too extensive for hope of cure by radical prostatectomy it was shown that 5 year survivorship varied widely from 59 per cent to 0 per cent depending on the presence or absence of hydronephrosis, bone metastases, and an elevated serum acid phosphatase level[1] These figures applied to patients treated by orchiectomy and estrogenic hormones who survived unassociated disease

In this study the influence of acid phosphatase levels on prognosis in advanced prostatic carcinoma was investigated An acid phosphatase level of 3 1 Gutman units or more was considered elevated, and a level of 3 0 or less was considered normal[2] [3] [4]

Sufficient data to allow analysis were available in the clinical records of 145 patients, all with well documented carcinoma of the prostate too advanced to allow radical prostatectomy All of these patients were treated by bilateral orchiectomy[5] followed by estrogenic hormones, usually stilbestrol, 5 mg daily

The incidence of normal and elevated acid phosphatase levels occurring in relation to the presence or absence of demonstrable osseous or lymphatic metastases is shown in table 1 These are in close agreement with the findings of Woodard and Dean[6]

## FATE OF PATIENTS WITH ELEVATED ACID PHOSPHATASE LEVELS BUT NOT METASTASES

It is apparent from table 1 that 33 patients had elevated serum acid phosphatase levels but without demonstrable bone or lymph node metastases The 5 year survivorship in this group is 31 per cent as compared to the group of 71 patients with normal acid phosphatase levels without metastases in whom the 5 year survival is 46 8 per cent These findings are consistent with the observations of Nesbit and Baum[7] who reported a 60 per cent incidence of death

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[2] Robinson, J W Gutman E B and Gutman A B Clinical significance of increased serum acid phosphatase in patients with bone metastases secondary to prostatic carcinoma J Urol 42 602–619 1939

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[6] Woodard H Q and Dean A L The significance of phosphatase findings in carcinoma of the prostate J Urol. 57 158–171 1947

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TABLE 1 *Incidence of normal and elevated acid phosphatase levels in relation to presence and absence of demonstrable bone or lymph node metastases in 145 patients with advanced prostatic carcinoma*

| | No Patients | Per Cent |
|---|---|---|
| Normal acid phosphatase with no demonstrable metastases | 71 | 49 |
| Normal acid phosphatase with demonstrable metastases | 13 | 9 |
| Elevated acid phosphatase with no demonstrable metastases | 33 | 22 7 |
| Elevated acid phosphatase with demonstrable metastases | 28 | 19 3 |
| | 145 | 100 |

from prostatic carcinoma within 3 years in patients with elevated acid phosphatase levels without metastases as compared to a 34 per cent incidence among the group with normal acid phosphatase levels

Among the 33 patients with elevated acid phosphatase levels subsequent serial x-ray and clinical examinations were obtained in twenty-two In 16 patients demonstrable metastases developed, thirteen within a 2-year period However, in 3 patients metastases were shown to develop as late as 3, 5, and 9 years following treatment It must be remembered that all these patients had the benefit of bilateral orchiectomy and stilbestrol therapy and it is reasonable to assume that this antiandrogenic treatment contributed to the delay in the appearance of metastases

It was noted that 6 patients showed no metastases during a period of observation extending up to 12 years

In 9 patients there were no sufficient serial x-ray examinations to allow satisfactory evaluation, and 2 patients had Paget's disease of bone with elevation in alkaline phosphatase and equivocal x-ray findings

### FATE OF PATIENTS WITH ELEVATED ACID PHOSPHATASE LEVELS AND METASTASES

Twenty-eight patients had bone metastases and elevated acid phosphatase levels

In this group 14 per cent survived 4 years or longer and 35 per cent survived 2 years or more following orchiectomy and stilbestrol therapy

These figures are to be compared with the findings in 13 patients who had normal acid phosphatase levels and metastases Here 23 per cent survived four or more years and 46 per cent survived 2 years or longer, showing that even in the group with metastases elevated acid phosphatase levels render the prognosis more grave

### CONCLUSIONS

If a patient with advanced prostatic carcinoma has no demonstrable bone or lymph node metastases but has an elevated acid phosphatase level, his chance for 5 year survival is significantly less than a patient with a normal acid phosphatase level, provided he is treated by orchiectomy and stilbestrol therapy and he survives unassociated disease

Seventy three per cent of patients with elevated serum acid phosphatase levels without demonstrable metastases will ultimately develop bone or lymph node metastases, four fifths of them within the ensuing 24 month period following orchiectomy and stilbestrol therapy

An elevated acid phosphatase level in patients with bone metastases is a poor prognostic sign and promises a lesser chance of 2 year and 4 year survivorship than does a normal acid phosphatase level, when treatment is bilateral orchiectomy and stilbestrol therapy

In this series of 145 patients, an elevated acid phosphatase level was found in 68 per cent of those having demonstrable bone or lymph node metastases and in 32 per cent of those without demonstrable bone or lymph node metastases

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# A CLINICAL STUDY OF A NEW RENAL FUNCTION TEST THE RADIOACTIVE DIODRAST RENOGRAM

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This paper describes the clinical investigation of a new tracer technique for rapid estimation of renal function, the radioactive diodrast renogram The test is performed externally by using gamma-ray scintillation counters to measure continuously the rates of accumulation and disappearance of $I^{131}$ labeled diodrast in the kidney areas, following an intravenous injection of the test material

One method employing $I^{131}$-tagged diodrast experimentally in the past (Oeser and Billion, 1952) was to measure the gamma-ray activity in urine samples following intravenous injection of the test agent The amounts excreted in the urine, when plotted graphically at timed intervals, gave curves indicative of overall renal tubular function, but provided no information about the function of each kidney separately unless the samples were collected by ureteral catheterization

The test procedure to be described in this report was developed originally through animal studies (Taplin, Meredith and Kade, 1955) and showed that the radioisotope technique was safe, and that it had potential usefulness in the diagnosis and management of patients with various urological disorders

The main purposes of this clinical investigation were 1) to devise the modifications in technique necessary to apply the test in patients, 2) to establish the normal pattern of the diodrast renogram by testing large numbers of individuals with normal kidney function and by comparing these records with those obtained from patients with various known renal disorders, 3) to determine the accuracy of the test by comparison with results from standard renal function tests, and finally 4) to evaluate the clinical applicability of the test especially in the field of urology

## MATERIALS AND EQUIPMENT

Commercially available preparations of radioactive diodrast, urokon and rose bengal* were diluted with sterile saline solution to the desired test concentration (30 μc/ml) Stable diodrast, urokon and hypaque solutions, as used for excretory urography, were also given in various concentrations to a number of patients to determine the influence of loading effects on the rates of uptake and secretion of the radioactive agents

Three sets of radiation detection and recording equipment were employed, one for each kidney and a third to measure the clearance rates of the $I^{131}$-labeled agents from the blood Each unit consisted of a gamma-ray scintillation counter

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Read at annual meeting, American Urological Association, Boston, Mass May 30, 1956

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*Note by editor* Doctor Winter's paper was awarded second prize in the essay competition sponsored annually by the American Urological Association's Committee on Scientific Research Dr Miley B Wesson, chairman

* Radioisotope Division of Abbott Laboratories, Oak Ridge, Tennessee

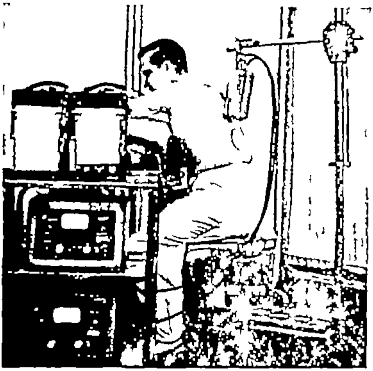

FIG 1 Two scintillation counters directed caudally toward kidneys are connected through rate meters to recorders

with a one inch thallium activated sodium iodide crystal connected through a rate meter to an Esterline Angus recorder The counters were housed in specially designed lead shields with adjustable mountings to achieve directional collimation and reduce background radioactivity (fig 1) A deep well scintillation counter was used to measure the gamma ray activity in blood and urine samples

## PRELIMINARY CLINICAL STUDIES

In rabbits, 30 microcurie doses (containing 0 1 to 20 mg/kg ) of both urokon and diodrast had been shown to be excreted rapidly and at nearly equal rates At the onset of this study, radioactive urokon was available and the first 20 patients were tested using this material Soon it was discovered that the rates of renal excretion of urokon were much slower in man than in animals Only 10 to 15 per cent of the injected dose could be recovered in the urine after 30 minutes, whereas in rabbits over 90 per cent is excreted in 30 minute urine samples After studying a few patients with one absent or nonfunctioning kidney and finding little difference between the slopes of the right and left renal excretion curves it was decided that the external measurements of renal clearance were reflecting little more than the decreasing levels of radioactive urokon in the blood Thus the radioactive urokon renogram (fig 2 upper) did not have the clinical applicability which was predicted from work in animals

After duplicating the test procedure using radioactive diodrast in one patient with a nonfunctioning left kidney and a normal right kidney who had been tested previously with radioactive urokon, it was immediately apparent that the normal diodrast renogram (fig 2, lower) was similar to that found in rabbits producing a distinctive pattern reflecting renal function It was then demonstrated that trace doses of radioactive diodrast were excreted by normal individuals at rates many times faster than the same subjects could excrete comparable trace doses of radioactive urokon These findings obtained externally were confirmed

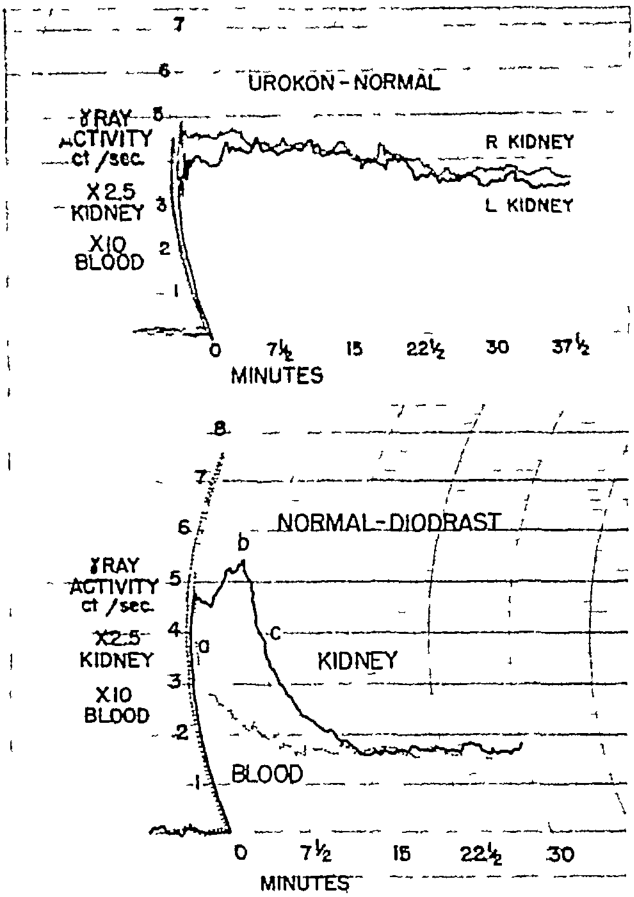

Fig 2 (Upper), radioactive urokon renograms lack characteristic pattern (Lower), normal radioactive diodrast renogram and blood clearance tracing

by measuring the per cent excretion of the injected material in fractional urine samples In addition, it was demonstrated that the rates of blood clearance of both radioactive test agents, as measured externally, correlated fairly accurately with values obtained simultaneously from radioassay of serial blood samples

In these pilot studies the importance of a number of technical factors became apparent In order to obtain reproducible results, it was necessary to localize the kidney areas accurately by examination of an upright roentgenogram of the abdominal region Second, in order to make comparative estimates of separate kidney function, it was essential to calibrate the instruments to respond equally to a standard radiation source of gamma rays and to place the counters in a manner which would permit measurement of equal volumes of tissue Third, it was soon noted that there was a slight difference between the excretion segment *c* of the right and left kidney curves

It was known that diodrast is absorbed and excreted partly by the liver, although it is mainly (85 to 90 per cent) recoverable in the urine Therefore, a series of experiments were performed to determine the optimal geometric conditions to obtain right renograms which are least affected by the liver Various positions

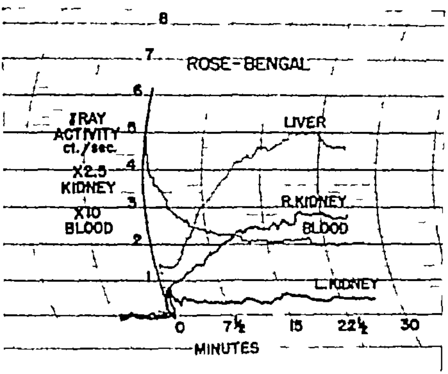

FIG 3 Radioactive rose bengal blood clearance curve normal hepatogram right and left renograms Liver radioactivity affects right renogram but not left

and angles were employed and the posterior upright position with the counters angled caudally toward both kidneys as shown in figure 1 was found most suitable

In an experiment to demonstrate the influence of the liver radioactivity on the right renogram, rose bengal $I^{131}$ was utilized This dye is known to be absorbed and excreted entirely by the liver and is not excreted by the kidneys In figure 3, a typical normal rose bengal liver curve is seen as well as the blood clearance tracing and bilateral rose bengal renograms It is apparent that the right and left kidney curves are different The right rose bengal renogram reflects and parallels to a lesser degree the hepatic curve due to recording radioactivity from the adjacent liver A demonstration that this material is not handled by the renal tubules is shown in the left rose bengal renogram

In another series of tests to evaluate the absorption secretion segment *b* of the normal diodrast renogram, the same subject under identical conditions but at separate times, was given equal doses of radioactive diodrast and rose bengal The superimposed left diodrast and rose bengal renograms demonstrated that the absorption-secretion segment *b* is absent in the rose bengal record

In the experiments where patients were given various doses of stable diodrast, hypaque and/or urokon prior to the radioactive test in order to assess the effects of overloading the kidneys, the following results were noted 1) slowing of the uptake secretory segment *b* of the radioactive diodrast renogram, while 2) urokon used in a similar manner induced a more rapidly declining excretory segment *c* in the radioactive urokon renogram

As a result of these preliminary investigations and special experiments designed to clarify the physiological meaning of the diodrast renogram, a standard technique was established and a large number of subjects were tested repeatedly to demonstrate the reproducibility of the test With the equipment used the optimal radioisotope dosage was 1 microcurie/3 kilograms of body weight In obese individuals the dosage is slightly higher, while in the asthenic person a reduction in dosage is necessary It should be noted for the benefit of others who might wish to use this test procedure that it is not only important to adhere to the techniques described, but to realize that modifications are likely to be necessary due to variations in sensitivity from slightly different types of instrumentation Furthermore, it is essential that the rate meters be recalibrated prior to each series of tests, and that the procedure must be performed first on a number of normal subjects, in order to establish a baseline from which one may interpret the significance of deviations from the patterns which occur in renograms from patients having various functional and/or structural abnormalities of the kidneys and ureters

## RESULTS AND INTERPRETATIONS

The results in this study are based on the performance and interpretation of 310 radioactive renograms In addition to 172 patients with a normal right or left kidney, radioactive diodrast renograms were performed in patients having the following urological disorders absent kidney, nonfunctioning kidney, ureteral obstruction with hydronephrosis, acute ureteral obstruction from calculus, hypoplastic kidney, nephrosclerosis, chronic glomerulonephritis, nephrotic syndrome, acute pyelonephritis, chronic pyelonephritis, polycystic kidneys, and neurogenic shock The radioactive renograms were correlated in each subject with one or more standard renal function tests such as creatinine, or para-aminohippuric acid clearance, phenolsulfonphthalein excretion, and excretory urography (table 1) With few exceptions, the laboratory studies on all patients also included blood counts, urinalysis, blood urea nitrogen, and blood creatinine determinations In some individuals, additional diagnostic procedures, such as retrograde pyelograms or aortograms were performed Furthermore, in many of the patients studied, the blood clearance of radioactive diodrast was determined from radioassay of blood samples obtained after 3, 10, 20 and 30 minutes, and by the external measurement of blood clearance using a third scintillation counter directed over the head or the left upper chest area These measurements were made to aid in evaluation of overall renal function and to compare the findings obtained with both techniques, and also to determine whether the external method would be feasible without subjecting the patients to repeated blood sampling The assayed 30-minute urine values obtained from 12 individuals with normal renograms averaged 57 per cent while the average value was 24 per cent from 11 individuals with abnormal renograms

1) *Normal diodrast renogram* A typical diodrast renogram for a normal left kidney, together with the record for blood clearance recorded simultaneously, is shown in figure 2, lower From inspection of the renogram, it is apparent that there are three main segments of the curve, whereas the blood curve shows an initial spike, followed by an exponential decline indicating the rate of disappearance of diodrast from the area tested (the head) In the diodrast renogram there is an initial sharp rise in activity immediately following injection of the radioactive diodrast with a peak *a* which represents the initial flood of radioactivity through

TABLE I *Comparison of radioactive diodrast renogram with standard renal function tests*

| | Diagnosis | Age | Diodrast Renogram (function) | Intravenous Urogram (function) | Blood Chemistry Urea N | Blood Chemistry Creatinine | Clearance Tests Creatinine | Clearance Tests PAH | (Right/left) PSP |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | (mg %) | | (ml/minute) | | (%) |
| 1 | No renal disease | 23 | Normal | Normal | 15 | 0.7 | 31/28‡ | ND | 4/4 (10 min)‡ |
| 2 | No renal disease | 61 | Normal | Normal | 14 | 1.1 | 115 | 580 | ND |
| 3 | No renal disease | 21 | Normal | ND | ND | 0.9 | 180 | 640 | ND |
| 4 | No renal disease | 28 | Normal | ND | ND | 1.5 | 120 | 610 | ND |
| 5 | No renal disease | 35 | Normal | Normal | 18 | 1.1 | 114 | ND | ND |
| 6 | Polycystic disease | 36 | Decreased | Decreased | 25 | 1.8 | ND | ND | 4/3 (20 min)‡<br>11% total 1 hr |
| 7 | Nephrosclerosis | 70 | Decreased | Normal | 21 | 1.2 | ND | ND | 4/5 (15 min)‡ |
| 8 | Nephrosclerosis | 60 | Decreased | ND | 27 | 1.5 | 50 | 160 | ND |
| 9 | Nephrosclerosis | 71 | Decreased | ND | 18 | 1.1 | 50 | 170 | ND |
| 10 | Hypertension | 44 | Decreased | Decreased | 35 | 2.1 | 62 | 207 | ND |
| 11 | Chronic glomerular nephritis | 24 | Decreased | Normal | 24 | 1.0 | ND | ND | 20% 1 hour<br>30% 2 hours |
| 12 | Congestive failure | 50 | Decreased | ND | 17 | 1.2 | 85 | 400 | ND |
| 13 | Congestive failure | 62 | Decreased | ND | 19 | 1.5 | ND | 230 | ND |
| 14 | Bilateral pyelonephritis and renal tumors | 58 | Decreased | † | 20 | 2.6 | 12.7/15.8‡ | ND | 5/6 (15 min)‡ |
| 15 | Bilateral hydronephrosis | 37 | Decreased | Decreased | 20 | 1.1 | 5.8/21‡ | ND | 7½/9½ (15 min)‡ |

ND means not done

* Normal value for creatinine clearance is over 100 ml/minute for para aminohippuric acid 400–800 ml/minute for phenolsulfonphthalein 40–60% in 1 hour and 60–85% in 2 hours

† Not performed because of elevated creatinine

‡ It is generally believed that individual renal blood clearance values are often reduced by the effects of cystoscopy ureteral catheterization and anesthesia

the kidney vessels and the vascular bed of the adjacent tissues. Immediately following this vascular peak, the curve rises again and forms a second dome (segment *b*). This segment is interpreted to represent the rate of active tubular cell uptake and secretion of diodrast into the kidney tubules and pelvis, and is superimposed upon the radioactivity in the vascular bed of the kidney area. It is seen that while the level of activity over the kidney is rising in the formation of segment *b* of the renogram that the blood is being cleared at an exceedingly rapid rate. *Thus, it is logical to deduce that this increase in radioactivity over the kidney is an index of active tubular cell secretion*, otherwise, this segment of the curve would parallel that of the blood. Segment *c* of the renogram is characterized by a precipitous fall in radioactivity reaching a plateau within 10 to 15 minutes in normal individuals. The slope of this segment indicates the patency of the upper urinary tract and freedom from urinary stasis.

There are minor variations in this typical pattern of the diodrast renogram. However, in all normal patients these three segments are readily distinguishable. *In young subjects the height of the initial spike a is usually higher than in elderly patients.* This variation is most likely due to differences in vascular capacity of the kidney. The slope and height of segment *b* are likewise more abrupt and higher in young normal individuals than in elderly patients and are probably related to variations in secretory function of the tubular epithelial cells. Segment *c* in the right diodrast renogram is usually slightly less steep and reaches a plateau at a higher level than that in the left renogram due to simultaneous recording of liver uptake of the material. *In most instances where there are marked differences between the right and left excretion segments c*, it has been found that these patients had a short, heavy type body build and/or enlargement of the liver.

2) *Nonfunctioning and/or absent kidney.* Typical renogram patterns in these abnormalities are shown in figure 4. Since in these conditions a minimal number or no tubular cells are available for diodrast uptake and secretion, only the vascular background is reflected in the curve by the abnormally low initial vascular

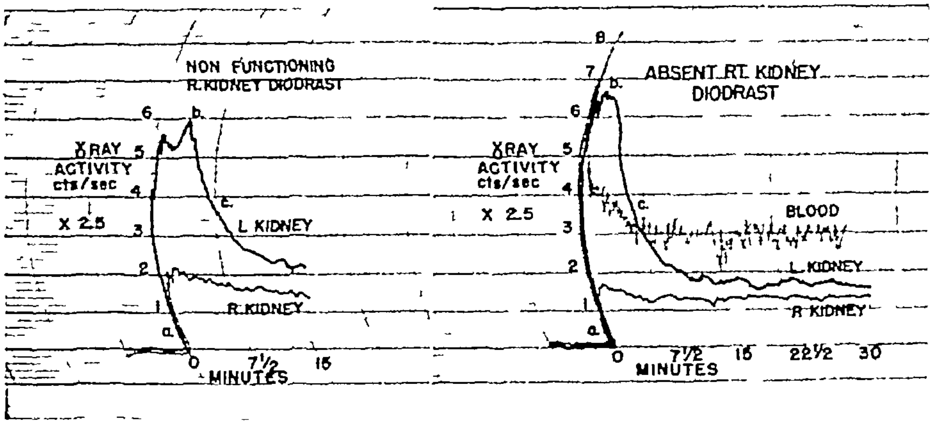

FIG 4 (Left) Vascular spike *a* is low, functional segment *b* and excretory segment *c* are absent in renogram of right nonfunctioning kidney (Right), lack of vascular amplitude, *a*, functional segment *b* and excretory component *c* characterize absent right kidney

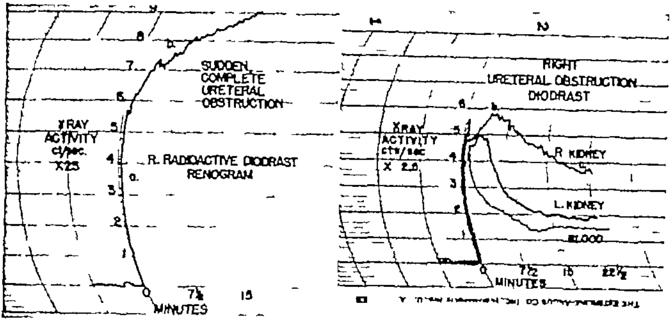

Fig 5 (Left) rapid ascent of segment *b* and lack of excretory component *c* are indicative of sudden complete ureteral obstruction (Right) prolongation of segment *b* and falling slowly excretory component *c* indicate partial right ureteral obstruction

spike *a*, an absent secretory segment *b* and a slowly falling excretory segment *c* It is interesting to note that the same pattern is obtained when a comparable dose of rose bengal is administered to a patient with normal kidney function (see fig 3, left renogram)

3) *Complete ureteral obstruction* A ureteral bag catheter was utilized to produce sudden complete ureteral obstruction An entirely different renogram pattern which may be considered to have diagnostic significance was found (fig 5, left) A characteristic feature of the curve in this condition is in segment *b* which continues to rise steadily as the radioactive material accumulates in the renal tubules and pelvis reflecting a high degree of ureteral obstruction In patients with ureteral calculus the curve rises *for 20 to 30 minutes or longer and finally reaches* a plateau which is interpreted to be an equilibrium resulting from several factors which include the rate of excretion from the opposite kidney, the rate of vascular reabsorption from the obstructed pelvis and tubules the rate of tubular secretion, and the rate of blood clearance Segment *c* is absent

4) *Partial ureteral obstruction and hydronephrosis* The diodrast renogram may also be considered to have diagnostic features in patients with this disorder (fig 5, right) The height of the initial *segment is related to the size of the renal* vascular bed In patients with chronic obstruction the initial vascular spike is usually abnormally low, probably resulting from associated decreased renal parenchyma and/or back pressure of urine The tubular secretory segment *b* is prolonged due to a decreased rate of removal of urine from the pelvis and associated impairment of tubular function Segment *c* is usually present, and its downward slope appears to be indicative primarily of the degree of ureteral patency

5) *Chronic nephritides* Only one patient with chronic glomerulonephritis was examined The pattern of the *diodrast renogram (fig 6 left) showed decreased* amplitude of the initial vascular segments The tubular secretion segments *b* *were prolonged* and the slopes in segments *c* were decreased The interpretation

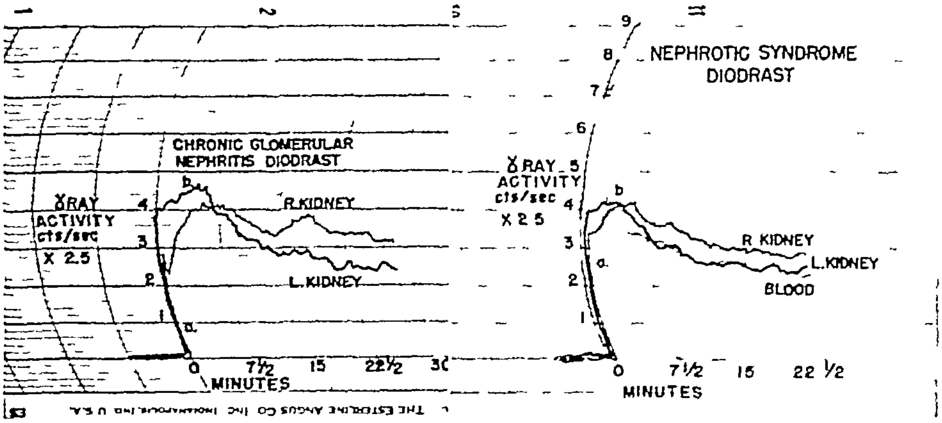

Fig 6

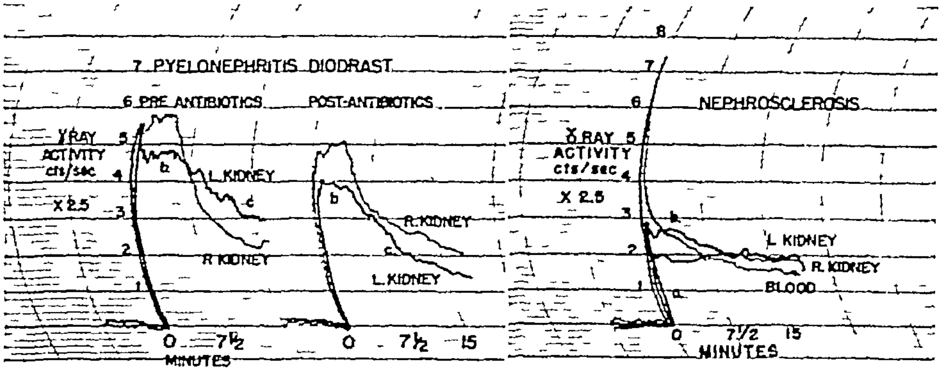

Fig 7 (Left), excretory segment *c* fell more precipitously after antibiotic therapy, right

of curves from such patients must remain tentative until more patients with chronic nephritis have been examined

A patient with the nephrotic syndrome was also examined The tracings presented in figure 6, right show decreased segments *a*, prolonged segments *b* and shallow slopes in segments *c* which parallel the rate of blood clearance These findings indicate diminished renal blood supply, and impairment of tubular cell secretion

6) *Acute pyelonephritis* In several individuals with unilateral acute pyelonephritis, abnormal renograms were obtained In a representative case (fig 7, left) there is a flattened prolongation of segment *b* for the left kidney, and the slope of segment *c* in this curve is diminished Following antibiotic therapy, the pattern of the entire curve returned toward normal indicating improvement in renal tubular cell function and renal excretion had occurred

7) *Nephrosclerosis* Several elderly patients having normal excretory pyelograms were tested Diodrast renograms in these patients consistently showed diminished initial vascular spikes *a*, absent or decreased functional segments *b*, and therefore abnormal excretory segments *c* A typical diodrast renogram for this condition is shown in figure 7, right

8) *Neurogenic shock* During this investigation neurogenic shock was observed

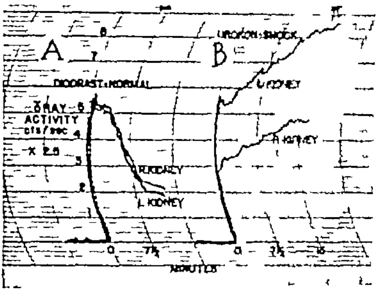

FIG 8 Neurogenic shock caused segments *b* to rise sharply as if sudden complete ureteral obstruction (see fig 5 left)

once while a patient was undergoing a urokon priming test A normal diodrast renogram had been obtained one day previously (fig 8, A) On this occasion repeated venipunctures with a No 20 gauge needle were made The patient appeared pale and apprehensive Soon after, a 25 ml dose of 70 per cent urokon containing 20 μc of $I^{131}$ labeled urokon was given intravenously While this test was in progress, the patient complained of faintness When his systolic blood pressure was found to be 50 mm of mercury, the test was terminated Inasmuch as he responded quickly to bed rest, the shock reaction was interpreted as neurogenic in origin However, the possibility of a urokon reaction could not be eliminated, although extensive clinical experience with urokon reactions (Winter, 1955) has shown that shock from urokon responds less rapidly and usually requires vigorous supportive therapy

The patient's glomeruli and tubules apparently continued to function, but the radioactive material continued to accumulate in the kidney areas instead of rapidly draining away through the ureters The most likely explanations for the record obtained (fig 8, *B*) are 1) accumulation of radioactive urokon in the kidney due to vascular changes which may cause depression of urine formation or 2) bilateral ureteral spasm caused by either neurogenic shock or a reaction to urokon Ureteral spasm has not been demonstrated previously in either of these conditions However, a similar radioactive renogram is found in patients with complete, acute ureteral obstruction due to calculus or inflated ureteral bag catheter (fig 5, left) and in experimental animals having bilateral surgical ligation of both ureters

9) *Hypertension due to renal disease* The following case report illustrates the value of the renogram in studying patients with hypertension and particularly the practicability in testing pediatric patients

A 6 month old white boy had severe acute gastroenteritis followed by transient coma, anuria and pyuria Subsequent examinations revealed a poorly functioning, infected left kidney and hypertension The blood pressure continued to rise until it reached 140/92 at 19 months of age At this age an aortogram showed absence of left renal artery filling while the right renal vasculature ap-

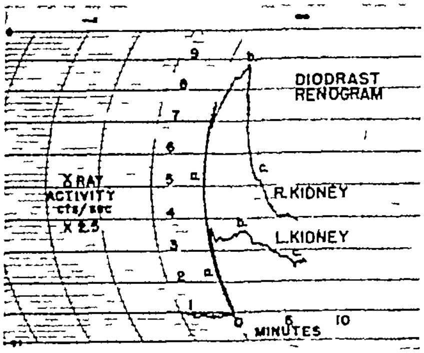

FIG. 9. Contracted pyelonephritic left kidney produced small vascular spike *a* and delayed, shallow functional segment *b*, indicating probable renal origin of hypertension in 19-month-old child.

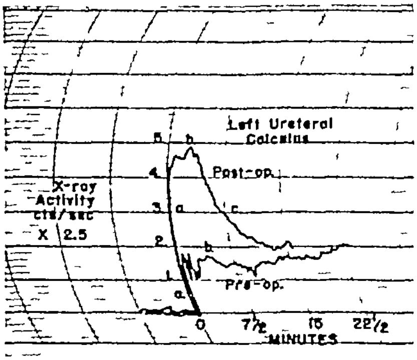

FIG. 10. Preoperative renogram indicating poor function and obstruction returned to normal after ureterolithotomy.

peared normal. The right renal shadow appeared enlarged and that kidney excreted contrast medium and indigo carmine normally. The contracted left kidney concentrated indigo carmine and contrast medium poorly. The baby was given a sedative and an 8-minute radioactive diodrast renogram performed (fig. 9). The right renogram appeared normal. However, the left vascular spike *a* appeared markedly diminished and a shallow, short functional segment *b* appeared belatedly. A 19.2 gm. left kidney was removed at surgery and microscopic sections revealed severe chronic pyelonephritis. The blood pressure gradually returned to lower levels (115/70) by the seventh day.

10) *Serial evaluation of renal function.* Renograms were performed pre- and postoperatively in several instances. A typical example is shown in figure 10. The preoperative left renogram demonstrated decreased vascularity *a*, function *b* and urinary stasis *c* due to a ureteral calculus. The post-ureterolithotomy renogram appeared normal.

## DISCUSSION

To the author's knowledge, no similar clinical radioisotope test procedures have been described for estimating the function of each kidney separately by external gamma-ray scintillation counting techniques. During the course of this investigation of the clinical applicability of the diodrast renogram, especially in urological practice, it became apparent that the test procedure has many potential applications in other fields of medicine, as well as being a suitable tool for further basic research in renal physiology

In internal medicine, this rapid test could be applied as a screening procedure particularly in young individuals with unexplained hypertension Under present conditions, all such patients must be subjected to a complete urological study which includes standard kidney function tests plus excretory urography and possibly cystoscopy and retrograde urography Inasmuch as only 5 to 10 per cent of patients with hypertension have a renal cause for their illness, a large number of individuals must undergo these complicated diagnostic procedures and obtain negative findings Since nearly all renal causes of hypertension are associated with functional impairment, the diodrast renogram should detect those individuals having renal dysfunction and separate them from those having normal function Thus, by using the diodrast renogram as a screening technique for hypertensives only those individuals having positive findings need be subjected to further urological diagnostic procedures

The applicability of this external test procedure at present has not been studied thoroughly in patients with various medical abnormalities of the kidney However, the results in this clinical urological study indicate that the diodrast renogram should provide a valuable index of separate kidney function in patients with nephritis and nephrosis particularly for the purpose of following the course of these disorders from the functional standpoint

In large clinics, hospitals, armed forces induction centers and large employment centers, the isotope test would be of value as a renal screening test similar to the accepted practice of taking routine chest roentgenograms

It should be emphasized that the techniques described in this report were developed to obtain *qualitative* estimates of renal tubular function, vascular capacity, and of ureteral patency, which appear to be sufficiently accurate for the purposes of this preliminary urological investigation When comparison is made between the interpretation of diodrast renograms and various standard biochemical indices of renal function, excretory urography and one or more renal clearance tests, good correlation is found to exist (table 1) In respect to further development of these external techniques for estimating overall or separate renal function, there are several possible modifications which could lead to the development of a rapid clinical and/or experimental procedure for the *quantitative* determination of renal tubular secretory function glomerular filtration rates and renal blood flow

*Advantages of the diodrast renogram* The diodrast renogram has many advantages over other methods of evaluating renal function

It is a rapid test requiring only 10 to 15 minutes for a patient with normal kidneys, and 20 to 30 minutes if renal disorders are present

The results are available immediately since the renogram is produced with recording instrumentation

The test may be performed at any time or place where electrical outlets are available

There is little to no patient discomfort (only one venipuncture with a small caliber needle is required)

No ill effects from the minute dose of diodrast (0 1 to 0 2 ml ) have been encountered in this study Although serious reactions to small quantities of diodrast (0 5–2 0 ml ) have been reported, the incidence is extremely rare (Pendergrass et al 1955)

It is less complicated to perform than the various renal clearance tests

It tests the function of each kidney separately without the necessity of cystoscopy and ureteral catheterization

Only one trained person is required to perform the test

No anesthesia is required

No special preparation of the patient is necessary Results are not invalidated by altered metabolic conditions, state of hydration, abdominal opacities or recent use of radioisotopes for other diagnostic purposes

It can supplement or be substituted for excretory urography in certain situations when blood urea nitrogen is elevated, x-ray facilities are not available, patient is too ill for x-ray examination, patient is not properly prepared or dehydrated, or patient is allergic to a large dose of contrast medium

It can supplement or be used in place of retrograde pyelography in certain situations ureteroenterostomy, uretero-neo-cystostomy, ureteral obstruction, cystoscopy impossible due to urethral obstruction and danger of infection and trauma from cystoscopy and retrograde ureteral catheterization

It may be repeated at frequent intervals to follow the course of various renal disorders

It can supplement aortography or replace it when not available where danger of complications from aortography does not warrant its use

The test agent is inexpensive At this writing radioactive diodrast may be obtained for $0 30 per twenty microcurie dose plus shipping costs

It lends itself to experimental investigation of the kidney Renal physiologists may find this external method of measuring the dynamic changes in renal blood flow and tubular cell function easier to perform than other more cumbersome methods now in use

*Disadvantages of the diodrast renogram* Several disadvantages are inherent in the radioactive renogram

The test is subject to errors of interpretation The most likely source of error is improper placement of scintillation counters in relation to kidney areas, and particularly interference from the liver when testing the right kidney Another cause of misinterpretation is overloading the renal tubular cells with contrast medium It is important therefore to delay performing the radioisotope test for several hours after an excretory urogram

The test does not give information about the possible causes of renal dysfunction

The initial expense of equipment ($1,800 00) is a disadvantage that may lessen in the future

At the present time physicians must be able to qualify regarding knowledge and use of $I^{131}$ before receiving a license from the Atomic Energy Commission to purchase the test materials for diagnostic use

Certain precautions are necessary in the use of $I^{131}$ tagged diodrast although the test doses and total amounts handled are small A personnel radiation monitoring service is considered essential in an isotope program *

## SUMMARY

The clinical applicability of a new radioisotope test for estimating individual renal function and ureteral patency with external gamma ray detection and recording equipment has been investigated in 216 patients having a wide variety of urological disorders Several modifications of the original technique of the test as used in animal studies were devised in adapting it for use in patients Characteristic renogram patterns were obtained from normal subjects and from patients with renal vascular and tubular dysfunction and with ureteral obstruction Directions for the performance and interpretation of radioactive diodrast renograms are discussed along with presentation of typical records

In urology, the test has the advantages of providing rapidly important information on renal function with negligible risk and discomfort to the patient It is useful as a screening test prior to complete urological study and as a means for determining functional changes pre- and postoperatively Its chief disadvantages are the initial expense of the equipment and occasionally aberrent records resulting from variations in geometry and placement of the counters and from minor electronic variables inherent in all sensitive radiation detection equipment The potential usefulness of the test in renal physiology and internal medicine has been discussed along with the definite possibility of further development of the test into a rapid clinical procedure which should provide quantitative data on renal function

The author wishes to thank Dr George V Taplin and his associates of the Atomic Energy Project, UCLA, for making possible this study through their generous aid, advice and provision of radiation materials and equipment The encouragement of Dr Willard E Goodwin, professor of urology UCLA, the co-operation of the VA resident staff of Dr Franz Bauer and his radioisotope service and the photographic contribution of Mr William Martinson and his staff were received with deep appreciation

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# INADEQUATE STERILIZATION OF CYSTOSCOPES

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During the conduct of the work of the Research Unit for Genito Urinary Tuberculosis, it quickly became apparent that the conventional methods most widely employed for the "sterilization" of cystoscopes were not adequate to kill M. tuberculosis within one hour. This suggested the possibility that cross-contamination might easily occur during routine cystoscopic examinations in any hospital, if the same cystoscope were used on a tuberculous patient and then used again on an uninfected patient, within one hour. The danger of such cross contamination is especially great because the diagnosis of urinary tuberculosis is often unsuspected at the time of the initial cystoscopic examination. It should be noted, incidentally, that there has been no decrease in the numbers of new cases of renal tuberculosis seen by the Veterans Administration in recent years.

Solutions which would be ideal for sterilizing cystoscopes should fulfill two requirements: a) The sterilizing solutions must not harm the soft cement which is used to hold cystoscope lenses and light bulbs in place, b) the sterilizing solutions should be able to kill all organisms, including M. tuberculosis, within one hour, so that the cystoscopes could be used again at the end of that time. Alcohol and phenol, for instance, are fine disinfectants but are damaging to the lens cement. These same factors would apply to any bronchoscopic instruments which contain soluble elements.

Tests were done on each of the agents used in these experiments to determine whether they were harmful to the cement. These tests were performed for us through the courtesy of Mr. Frederick J. Wallace, president of American Cystoscope Makers, Inc. The "sterilizing" effects of these agents were then studied on groups of artificially contaminated cystoscopes. The "sterilization" methods tested included those used routinely by practically all hospitals of which we know. These controlled experiments were carried out repeatedly, during the past 2 years.

## METHODS

Freshly isolated cultures of pathogenic M. tuberculosis were homogenized and suspended in saline in estimated wet weight concentrations of from 0.5 to 1.5 mg. per cc. Groups of six sterile cystoscopes were heavily seeded with this suspension, both inside and outside the lumina. Except for one control cystoscope from each group, the contaminated cystoscopes were immersed in the solutions to be tested, for various periods of time. The action of the test solutions was stopped at the end of the test period by copious rinsing of the cystoscopes

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under running water, including the control cystoscope Each cystoscope was then flushed systematically with 5 cc sterile saline, and five tubes of ATS medium were each inoculated with 1 cc saline which had been used to flush the cystoscopes The culture tubes were then observed for eight weeks

## RESULTS

Several solutions were found to be ineffective for killing M tuberculosis Solutions of mercuric oxycyanide, in concentrations of 1 1000, 1 500 and even 1 100, would not kill M tuberculosis under these conditions, within one hour It was also found that solutions of the quaternary ammonium compounds, widely advertised for the "sterilizing" of cystoscopes, were not capable of killing M tuberculosis, even in the most concentrated form suggested by the makers Iodine and chlorine releasing agents did not kill M tuberculosis in one hour, under these conditions Formalin vapor cabinets were ineffectual in killing M tuberculosis within one hour (formalin vapor cabinets did not even kill B proteus in one hour) Washing and immersion in liquid soap solutions for one hour did not dislodge or kill the organisms of M tuberculosis

Our conclusions were that immersion of the instruments in 10 per cent formalin solution for 5 minutes was the best method for killing M tuberculosis on cystoscopes It appeared advisable to wash the surfaces and lumina (with all stopcocks open, of course) with warm soapy water before immersion in formalin In this way gross organic debris was removed, which might otherwise become hardened upon the instrument by the action of the formalin, and which might protect M tuberculosis from the germicidal action

The formalin solution must be washed from the instruments before they are used, lest it burn the urethra The instrument can then be stored in oxycyanide or a quaternary ammonium solution until the next patient is ready For instances where formalin cannot be used (because of skin allergy on the part of personnel) instruments can be soaked for several hours in solutions such as the instrument germicide made by the Lehn and Fink Company Instruments must be immersed for several hours in this solution, then washed off and stored in any other mild antiseptic solution such as oxycyanide 1 1000 This germicide has the advantage of containing soaps, which help to cleanse the instruments, but is less dependable than the formalin

## URETERAL CATHETERS

The sterilization of ureteral catheters was found to be difficult when solutions or vapor cabinets were used, since the narrow lumina were not thoroughly exposed to the disinfectant It was found best to flush the catheters through with 20 cc warm, soapy water and then boil them for 5 minutes in order to clear all tubercle bacilli from them They were then stored in oxycyanide 1 1000

## DISCUSSION

The seeding of our cystoscopes with M tuberculosis, for these experiments, was probably done with numbers of organisms many times heavier than those encountered in clinical practice We believed, however, that this was necessary, since our experiments required a large safety factor Since a rinsing of the cystoscopes was always included in each study, the actual number of organisms involved was far smaller than the original number of the organisms in the inoculum Under clinical conditions, one would expect organisms imbedded in mucus and other organical matter to cling to a cystoscope more than organisms emulsified in saline, as were ours In order to credit a germicide under experimentation with favorable results, the rinsed control cystoscopes had to show growth of tubercle bacilli, and this could be observed in 100 per cent of the experiments only when the original seeding was made with a heavy inoculum Furthermore, the action of a good germicide should not be limited to the relative number of organisms exposed to it

## SUMMARY

Oxycyanide solutions, solutions of quaternary ammonium compounds, iodine compounds, chlorine releasing compounds and formalin vapor cabinets were all found to be ineffectual for sterilizing cystoscopes contaminated with M tuberculosis, within 1 hour Immersion in 10 per cent formalin solutions for 5 minutes was found to be effective in killing all bacteria on cystoscopes inoculated with M tuberculosis Lehn and Fink instrument germicide was also found to [illegible] but only after several hours of immersion It was found [illegible] debris from all instruments before disinfection was attempted It was found necessary to wash all strong disinfecting solutions from the instrument before they were introduced, lest the patient's urethra be burned

Any instruments which could be boiled (such as ureteral catheters) were best sterilized by boiling Instruments which did not contain soft cement could be sterilized by soaking in 70 per cent alcohol, which is tuberculocidal

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# A SELF-MANAGED BLADDER TRAINING DEVICE FOR TETRAPLEGICS

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In the treatment of spinal cord injuries every effort is made to make the patient independent In the treatment of a spinal cord injury, all patients are placed on bladder training for "conditioning of the reflex",[1] prevention of bladder contraction[2] and psychological purposes [2] This bladder training unit was made in order to aid quadriplegics who are extremely helpless

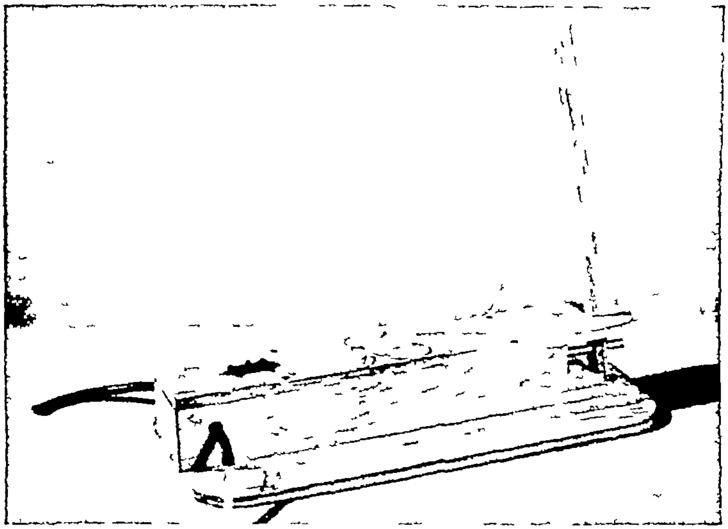

FIG 1 Glass connector is attached to patient's catheter Other end is connected to bottle on floor

The device has a twofold purpose a) bladder training can be performed by the tetraplegic without calling a nurse or attendant to clamp or unclamp his catheter, a marked psychological benefit and b) it saves man-hours for personnel involved in patient care

Since many patients with cervical lesions are disturbed by paroxysmal hypertension due to bladder distension,[3] the catheter must be released as soon symptoms appear Nurses or attendants may be occupied at the moment other patient-care problems and therefore may be unable to respond immedi at the patient's request With this device, the patient can release the con

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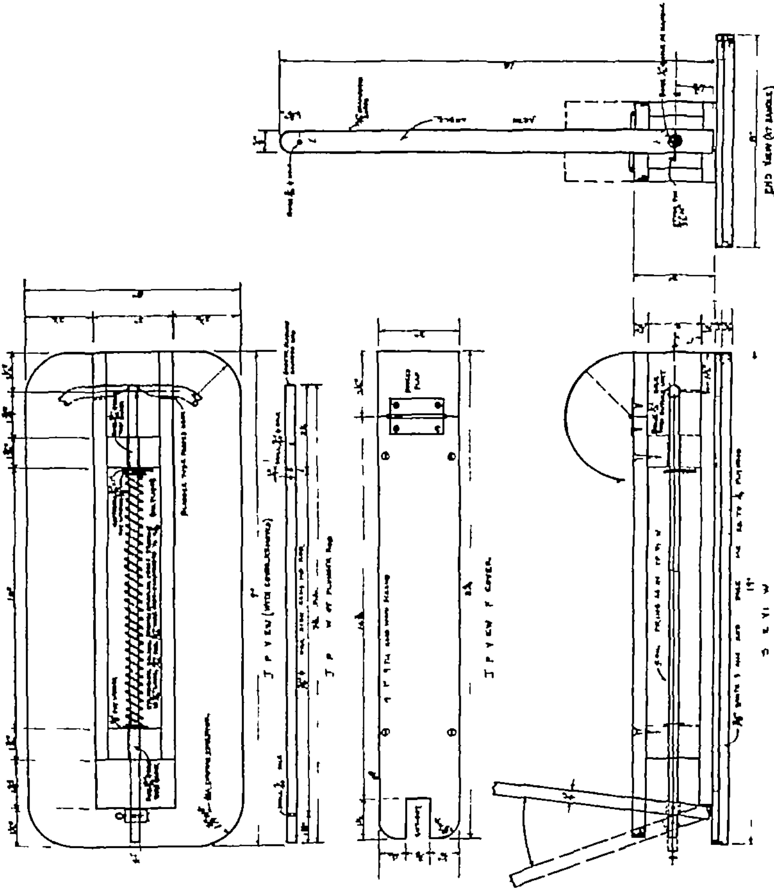

FIG 2 Detailed plans for quadriplegic bladder training device

the bladder before he becomes uncomfortable Furthermore, he can gradually attempt to overcome the relatively short periods between paroxysms of hypertension by managing the bladder himself

As long as the patient has some elbow function (flexion), he can manage the activating handle

The string at the top of the activating handle (fig 1) can be attached tautly to the head of the bed To this string another string is tied and suspended to within reach of the patient's mouth By turning the head after the string is in the patient's mouth, the patient with totally paralyzed upper extremities can release the bladder contents This latter procedure requires that the strings be carefully arranged after the unit has been firmly attached to the bed

## DESCRIPTION

Figure 1 shows the device which can be placed in bed beside the patient Figure 2 shows the detailed plans

## SUMMARY

A self-managed bladder training device which serves a twofold purpose in the constant endeavor to guide the quadriplegic patient toward self-dependency is described

The author wishes to express his appreciation to Mr Alvin Roberts, G U technician, the Engineering Department and Medical Illustration Department of V.A Hospital, Long Beach, Calif

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# A PLASTIC SCROTAL BRIDGE

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Bed rest and scrotal support are often necessary adjuncts in the treatment of many urological conditions of the scrotum and its contents. Recently we have utilized a plastic scrotal bridge, which is light, rigid, durable, easy to clean, and can be made in less than twenty minutes in a hospital maintenance shop. It is practical and useful.

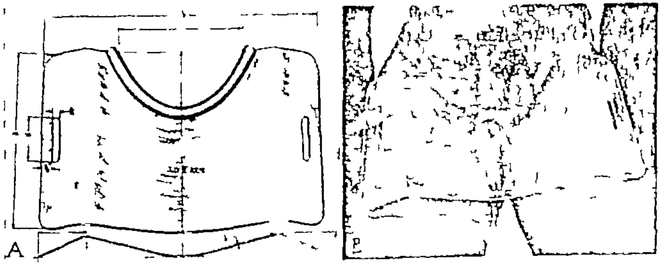

FIG. 1

The material used is ⅛ inch thick plexiglas, a commercially available plastic product, which is cut to conform to the dimensions shown in figure 1, *A*, using ordinary workshop tools. The central concave and lateral convex curves are made by placing the area to be formed over a gas flame or electric heating element until soft and pliable, gently bending it to the desired curve, and then quickly immersing the plastic appliance in cold water. A strip of soft rubber tubing, one wall of which has been longitudinally cut and fitted over the scrotal edge of the plastic support, is used as a rubber bumper between bridge and scrotum. The finished product as it appears on a patient is illustrated in figure 1, *B*.

It is suggested that the patient's thighs and scrotum be separated from the plastic bridge by a thin layer of gauze to prevent excessive local diaphoresis. The appliance may be gently secured to the patient during the night by means of elastic bandage, roller gauze, cloth strapping, or adhesive tape utilizing the lateral slits of the bridge as anchoring points.

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# IMPROVED ANALGESIA WITH NISENTIL AND LEVALLORPHAN IN UROLOGICAL PROCEDURES

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In our report on a previous study, we described the merits of nisentil as a urological analgesic [1] In this followup study we report the analgesic and sedative effects from increased nisentil dosage with a new narcotic antagonist

In an attempt to obtain greater analgesia without increasing sedation, we used nisentil in combination with levallorphan Levallorphan was chosen after reference to work done by Cullen and Santos[2] with levallorphan tartrate (3 hydroxy-N-allylmorphinan tartrate) used as a narcotic antagonist They found that this drug minimized respiratory depression when used simultaneously with the narcotic, levo-dromoran

## METHOD

We began our study using a 60 1 ratio intravenously, i e , 60 parts nisentil to 1 part of levallorphan Two patients were given 30 mg of nisentil and 0 5 mg of levallorphan Neither good analgesia nor sedation resulted from this combination

A second group (5 patients) was given the same ratio intravenously with the dosage increased to 60 mg of nisentil and 1 mg of levallorphan The resulting severe reactions included aggravated pain, vomiting, complete exhaustion and deep post-reactive sedation lasting as long as six hours

A combination of 60 mg of nisentil and 0 5 mg of levallorphan was used on six other patients No sedative action was noted in any of these patients However, there was fair analgesia in 5 patients and good analgesia in one Seventy-four urological patients were then chosen at random for a study in which the dosage ratio was 60 mg of nisentil to 0 25 mg of levallorphan The age range was from 34 to 90 with the average of 59 1 years Seventy-one were males and three were females Forty-one had a history of cardiac disease A mixture of 60 mg of nisentil and 0 25 mg of levallorphan was administered intravenously to all patients The drugs were used in their concentrated form, and all injections were completed in 30 seconds Three different urological procedures were done in the following distribution

*Urological procedure distribution for 60 mg nisentil 0.25 mg levallorphan study*

| Procedure | No of Patients |
|---|---|
| Cystopanendoscopy | 37 |
| Cystoretrograde | 34 |
| Perirenal air insufflation | 3 |
| Total | 74 |

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## RESULTS

Of these 74 cases, 70 had good analgesia and 4 had moderate analgesia There were *no cases of poor analgesia, as all of the patients had* analgesia within 3 minutes after the injection was completed As in the preceding study on nisentil, analgesia was considered good when the urological procedure was accomplished with no complaint from the patient, moderate when the patient complained of some discomfort, but permitted completion of the procedure and poor when the patient did not allow the procedure to be completed

*Analgesia results for 60 mg nisentil 0.25 mg levallorphan study*

| Analgesic Effect | No. of Cases | Per Cent of Cases |
|---|---|---|
| Good | 71 | 95.9 |
| Moderate | 3 | 4.1 |
| Poor | 0 | 0 |

It was necessary to repeat cystoretrograde studies on 3 patients who had good analgesia Their second dosage ratio was 60 mg of nisentil 0.5 mg of levallorphan *In each case the second procedure was recorded as a moderate analgesic* result

In all 74 cases there was complete recovery from the sedative effect within 30 minutes All patients were lucid and responded to all questions during the procedures Unpleasant side effects such as nausea, vomiting itching, and drug idiosyncrasies were absent in all the cases There were no appreciable changes noted in blood pressure, pulse, or respiration

Thirty nine patients did experience some dizziness The dizziness was rather mild and was particularly noted when the patients changed from the supine to the sitting and upright positions *In no case did the dizziness last* more than 14 minutes All patients were completely ambulatory within 30 minutes after the injection was given No serious untoward reactions were encountered in any case

## SUMMARY

To increase the analgesic effects of nisentil, 60 mg (twice the amount previously recommended), was given to 74 patients The increased dosage of nisentil was mixed with 0.25 mg of levallorphan a narcotic antagonist, to allay any possible undesirable side effects Various urological procedures were carried out *Good analgesic results were obtained in 71 cases (95.9 per cent) and moderate* analgesic results in 3 cases (4.1 per cent) Mild nauseous dizziness was noted in 39 cases

The combination of nisentil and levallorphan in a 60 mg 0.25 mg proportion gives a very mild sedative action It permits the urologist to conduct many office urological procedures with no discomfort to the patient and yet allows the patient to be lucid and ambulatory within 30 to 40 minutes after the drug is given

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*From the Urological Service, Lincoln Hospital, New York, N. Y.*

In our report on a previous study, we described the merits of nisentil as a urological analgesic.[1] In this followup study we report the analgesic and sedative effects from increased nisentil dosage with a new narcotic antagonist.

In an attempt to obtain greater analgesia without increasing sedation, we used nisentil in combination with levallorphan. Levallorphan was chosen after reference to work done by Cullen and Santos[2] with levallorphan tartrate (3 hydroxy-N-allylmorphinan tartrate) used as a narcotic antagonist. They found that this drug minimized respiratory depression when used simultaneously with the narcotic, levo-dromoran.

## METHOD

We began our study using a 60:1 ratio intravenously, i.e., 60 parts nisentil to 1 part of levallorphan. Two patients were given 30 mg. of nisentil and 0.5 mg. of levallorphan. Neither good analgesia nor sedation resulted from this combination.

A second group (5 patients) was given the same ratio intravenously with the dosage increased to 60 mg. of nisentil and 1 mg. of levallorphan. The resulting severe reactions included aggravated pain, vomiting, complete exhaustion and deep post-reactive sedation lasting as long as six hours.

A combination of 60 mg. of nisentil and 0.5 mg. of levallorphan was used on six other patients. No sedative action was noted in any of these patients. However, there was fair analgesia in 5 patients and good analgesia in one. Seventy-four urological patients were then chosen at random for a study in which the dosage ratio was 60 mg. of nisentil to 0.25 mg. of levallorphan. The age range was from 34 to 90 with the average of 59.1 years. Seventy-one were males and three were females. Forty-one had a history of cardiac disease. A mixture of 60 mg. of nisentil and 0.25 mg. of levallorphan was administered intravenously to all patients. The drugs were used in their concentrated form, and all injections were completed in 30 seconds. Three different urological procedures were done in the following distribution:

*Urological procedure distribution for 60 mg. nisentil 0.25 mg. levallorphan study*

| Procedure | No. of Patients |
|---|---|
| Cystopanendoscopy | 37 |
| Cystoretrograde | 34 |
| Perirenal air insufflation | 3 |
| Total | 74 |

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Accepted March 1, 1956.

[1] Garnes, H. A.: Analgesic effect of nisentil in various urological procedures. J. Urol., 74: 567–569, 1955.

[2] Cullen, S. C. and Santos, C. C.: Analgesia for chronic pain without respiratory depression. A. M. A. Arch. Surg., 69: 410–414, 1954.

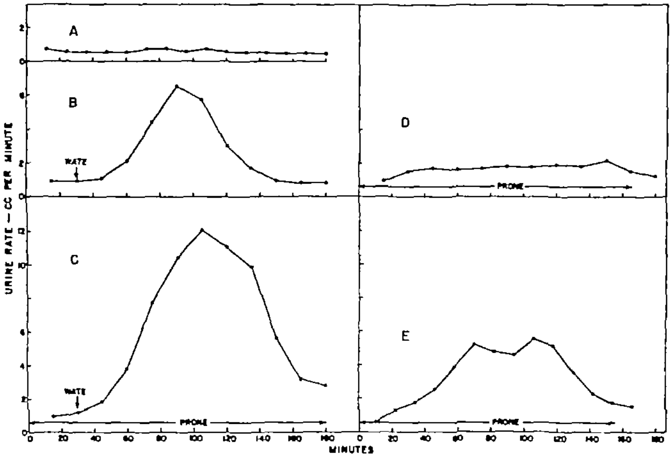

FIG 1 Urine output in man A during routine laboratory activity B and C after 500 cc water by mouth subject upright in *B* prone in *C* *D* and *E* after 8 and 19 conditioning experiments respectively

in the rate as the experiment progressed Curves B and C depict the diuresis that resulted from the ingestion of 500 cc water The diuretic response is greater in the horizontal than in the upright position, a finding reported by other investigators [1-4] These two experiments are presented primarily for comparison with the diuretic responses seen in subsequent experiments

Curve D of figure 1 is a record of the urine output of the subject in the prone position without water This experiment follows 8 previous experiments in which he ingested 500 cc of water while in the prone position Although the urine rate at the end of the first hour is about 80 per cent greater than that of the first 15 minute period, the increase is not so great, or so sudden in onset, as that seen in curve E, which illustrates the urine response occurring after an additional 9 experiments had been run continuing the water ingestion in the prone position In curve E the urine rate increased from 0 6 cc to a peak of 5.2 cc per minute, and then receded toward the control rate This is the first experiment in which a renal response of such magnitude occurred on merely assuming the horizontal position and because this diuresis is similar to one occurring after the ingestion of water it is called a pseudo-water diuresis

Curve A of figure 2 illustrates the urine volume response to the supine position Here again the rate increased while the subject was horizontal, from 0 9

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Accepted for publication January 26 1956

[1] Brun C Knudsen E O E and Raaschou F Acta Med Scand 122 315 1945

[2] Ni T G and Rehberg P B J Physiol 71 331-339 1931

[3] Smith H W Univ of Kan Lectures p 58 1943

[4] White H L Rosen I T Fischer S S and Wood G H Am J Physiol 78 185-200 1926

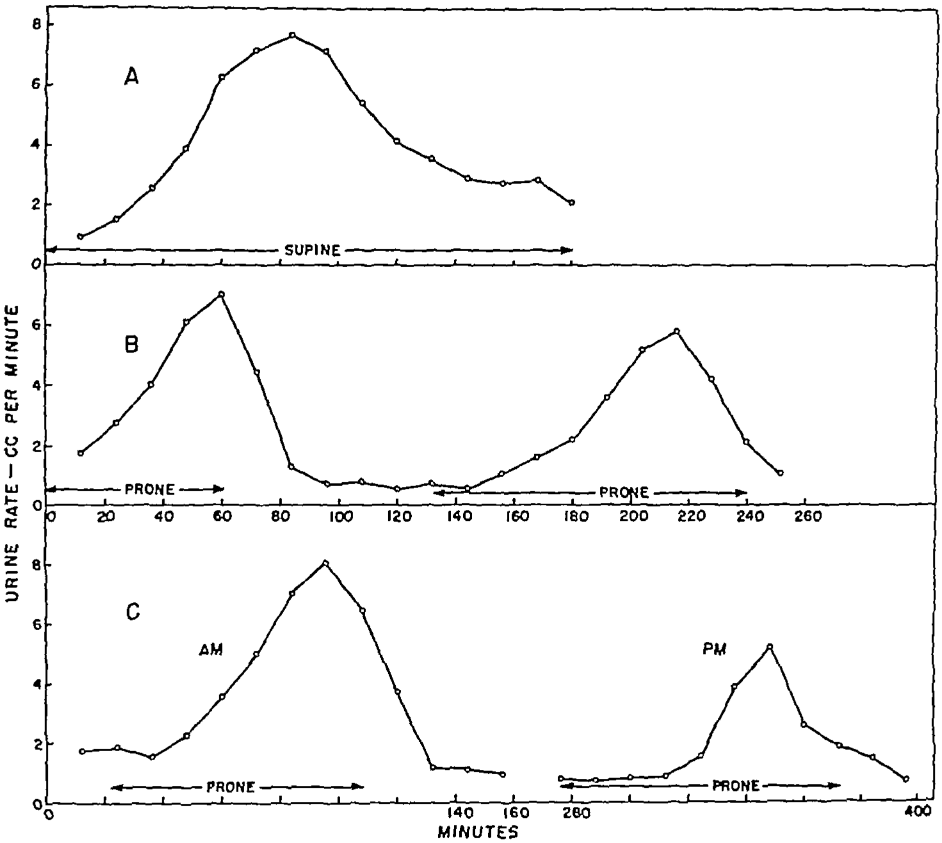

Fig 2 *Pseudo-water diuresis in man A, subject supine B, two experiments in same morning C, one experiment in morning and one in afternoon, same day*

to 7 7 cc per minute Apparently there was no difference in the urine output with the assumption of the prone or supine position Because the experiments which stimulated the present investigation were carried out with the subject prone only a few of the experiments here reported were performed with the subject supine

Curve B of figure 2 is a record of the volume response to the prone position when it was assumed twice within a period of 4 hours This experiment shows that the diuresis can occur repeatedly, and that it is interrupted quickly by the erect posture The same response was seen when the prone position was assumed 3 times in the course of a morning's run, the erect posture being assumed as soon as an increase in the urine rate was observed even though the prone rate had not reached its maximum

If the prone position was assumed in the morning and afternoon, with fluid intake limited to 300 cc tea at lunch between experiments, diuresis occurred in the afternoon just as it did in the morning but the magnitude was not as great (curve C, fig 2) When only an afternoon experiment was run diuresis similar to the second one of curve C occurred but the diuresis was appreciably greater

Because of the role the antidiuretic hormone (ADH) plays in water metabo-

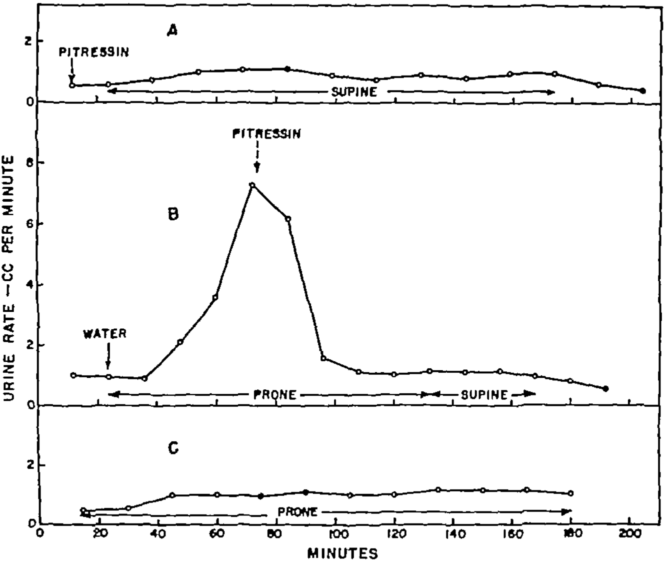

FIG 3 Urine output in man *A* inhibition of pseudo water (postural) diuresis by pitressin *B*, inhibition of combined water and pseudo-water diuresis by pitressin *C* inhibition of pseudo water (postural) diuresis by dehydration

ism, it was deemed advisable to see whether the hormone could inhibit the pseudo-water diuresis Curve A of figure 3 illustrates the inhibition of the initial diuresis by the subcutaneous injection of 8 pressor units of pitressin (Parke Davis) It must be pointed out that even though the greater initial diuresis was inhibited by pitressin the prone urine rate was higher than that in the erect posture as long as the subject remained in the horizontal position

Can the combined action of posture and the ingestion of water be overcome by an injection of ADH? Curve B shows that the diuresis resulting from this dual procedure is inhibited but that the urine rate in the horizontal position is again higher than the rate after the erect posture is assumed

The subcutaneous injection of 8 units of pitressin probably results in a blood concentration much higher than that occurring physiologically For this reason it was thought of some importance to see whether a normal increase in the ADH concentration of the blood could inhibit the pseudo-water diuresis Two experiments were run in which the subject limited his fluid intake for 24 hours to the point where he was extremely uncomfortable because of thirst Curve C, figure 3, is a record of the urine rate of the experiment in which the thirst was more severe The magnitude of the diuresis was definitely inhibited although the prone urine rate was still approximately double that occurring in the erect pos ture In the second dehydration experiment the thirst was not so severe and the inhibition of the diuresis, although definite, was not so great

To determine whether the laboratory surroundings were necessary for the pseudo-water diuresis to occur, and whether the diuresis can occur at night, 3 experiments were done outside of the laboratory, one in the morning and 2 at midnight, the latter began at midnight and lasted for 3 hours with 15-minute collection periods In all 3 experiments the urine rate increased in the horizontal posture but the magnitude of the diuresis was not so great as it was in the laboratory

In all of the experiments the urine during the pseudo-water diuresis paled just as it did from true water diuresis In one experiment in which the urine concentration was determined, the urine decreased in total concentration from a control of 840 to a low reading at the height of diuresis of 200 milliosmols per liter

## DISCUSSION

In the investigations in which it was reported that water diuresis is greater in the horizontal than in the erect position,[1 4] the initial volume of water ingested to induce diuresis was followed by smaller volumes at regular intervals to sustain the diuresis during the experiment The decreased urine output occurring in the upright position (standing quietly or on a tilt-table) was attributed to a decrease in renal blood flow and glomerular filtration and to the hemoconcentration that occur when the subject is kept motionless in the erect posture[1 5] These hemodynamic factors are also accompanied by changes in the secretion of ADH such that there is an increase in blood ADH concentration, actuated perhaps by the pressoreceptors[1]

The rapidity with which the diuresis occurred in the present investigation suggests that a vascular mechanism is involved that brings about the increase in urine rate when the subject is prone But the experiment illustrated by curve D, figure 1, does not show the large initial diuresis seen in later experiments, although the vascular responses to the horizontal position must have been the same in this experiment as in later ones Unfortunately, no control experiment of long duration was carried out in which the urine rate was determined in the horizontal position However, in the 8 experiments preceding the one illustrated by curve D, figure 1, the second 12-minute urine volume in the prone position before the ingestion of water showed no significant increase from that of the first Although this is not an adequate control it is of importance in the light of succeeding experiments in which there was an appreciable increase of the second prone urine volume over that of the first in the majority of experiments

There are two mechanisms that bring about the increased urine volume in the horizontal position in the present investigation The first is made up of the hemodynamic factors mentioned above These factors increase the glomerular filtration in the horizontal position and probably account for the moderate but definite increase in urine rate seen near the end of the experiments while the

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[5] Brun, C , Knudsen, E O E and Raaschou, F Acta Med Scand , **122** 332-341, 1945

subject is in the horizontal position The decrease in urine rate immediately after the subject assumes the erect position can be attributed to changes in these hemodynamic factors These same blood and vascular changes in all likelihood account for the moderate increase in urine output in the horizontal position in the pitressin and in the dehydration experiments of figure 3

Superimposed upon the moderate diuresis, and masking it is the initial, and greater, diuresis that occurred when the subject assumed the horizontal position This diuresis may be explained on the basis of a conditioned reflex Although there was no preconceived idea of conditioning the renal response, nevertheless after 17 water diuresis experiments had been run, the mere assumption of the horizontal position resulted in a large increase in the urine output The time course of this initial diuresis is very much like that of true water diuresis, but the magnitude is not so great as the response to the ingestion of water in the prone position This is evident when one compares figure 1, curve C with the pseudo-water diuretic curves of figures 1, *E* and 2, *A*, *B* and *C*

Experiments in which conditioned water diureses occurred have been reported by Marx[6] and by Bykow and Alexejew Berkman[7] Marx stated that one dog out of 4 responded with diuresis to the sounding of a musical note or to the laboratory surroundings, after several months of training which consisted of tying the dog in the same room, sounding a musical note and placing a pan of diluted milk in front of the animal Bykow and Alexejew Berkman observed that in one dog the rectal infusion and immediate withdrawal of water, the introduction of a rectal catheter or simply placing the dog in the experimental stall resulted in an increase in urine flow very much like that observed during a period of conditioning consisting of the repeated rectal infusion and subsequent absorption of the water The increased urine rates in these two reports were attributed to the conditioned inhibition of the ADH secretion by the previous training The nerve supply to the kidney is not necessary for this diuresis because similar results were seen in the denervated kidney of a dog[8]

## SUMMARY

The assumption of the horizontal (prone or supine) position by a normal male subject induced an initial and sudden increase in urine output as much as 6 times the control rate This diuresis followed the time course of water diuresis and occurred in 34 out of 36 experiments The diuresis is attributed primarily to a conditioned inhibition of the secretion of the ADH of the posterior pituitary, the conditioned reflex resulting from the ingestion of 500 cc of water while the subject was in the horizontal position on 17 occasions prior to the first appearance of the pseudo-water diuresis

[6] Marx H Am J Physiol **96**. 356–362 1931

[7] Bykow K M and Alexejew Berkman I A Pflug Arch. **224** 710–721 1930

[8] Bykow K M and Alexejew Berkman I A Pflug Arch **227** 301–308 1931

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*Southeastern*—Atlanta, Ga. April 7-11 1957

*Note by editor* A complete list of the executive committees of the various sections, and a complete list of the officers and members of the executive committees of the various branch societies will be printed in the December 1956 issue

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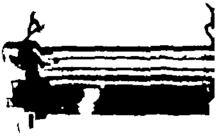

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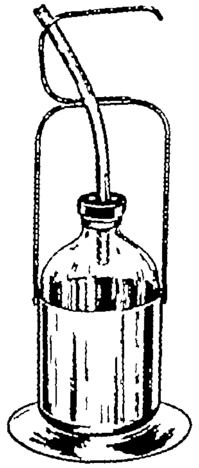

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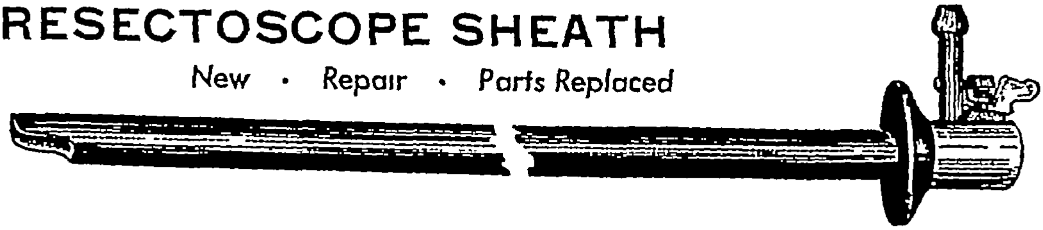

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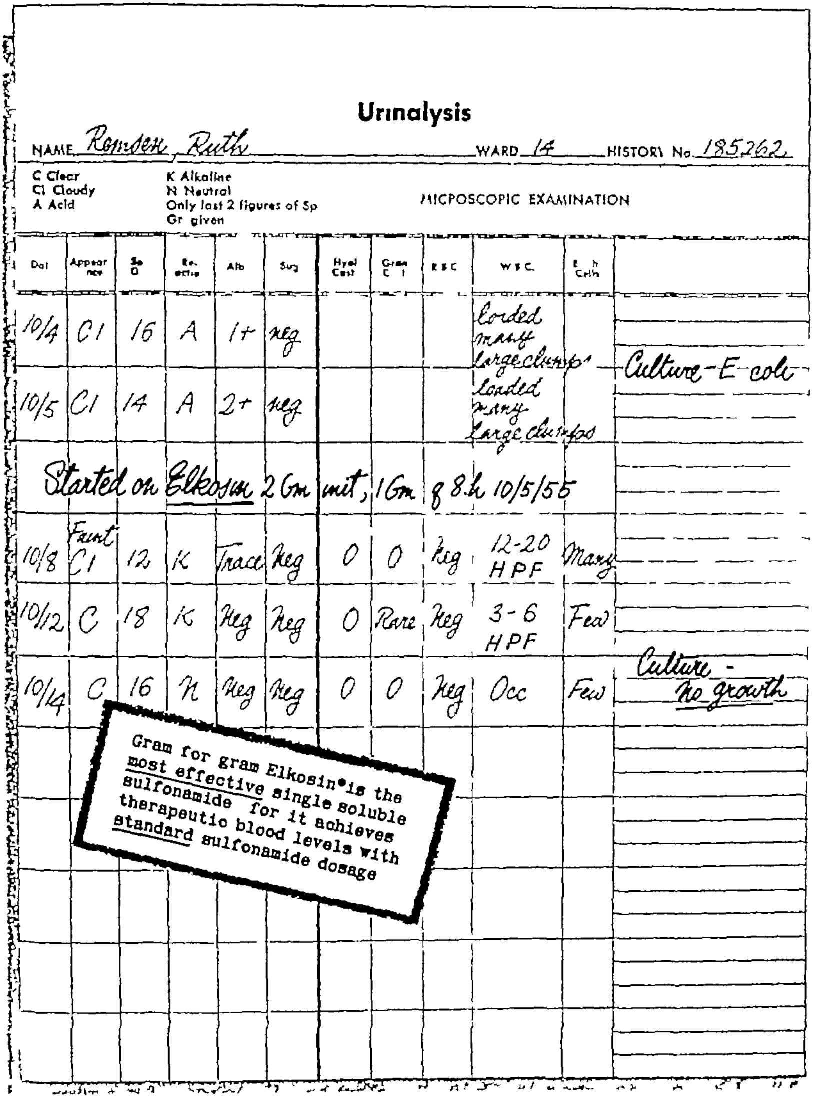

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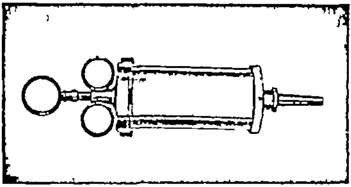

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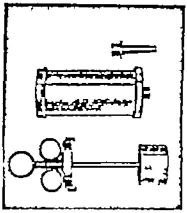

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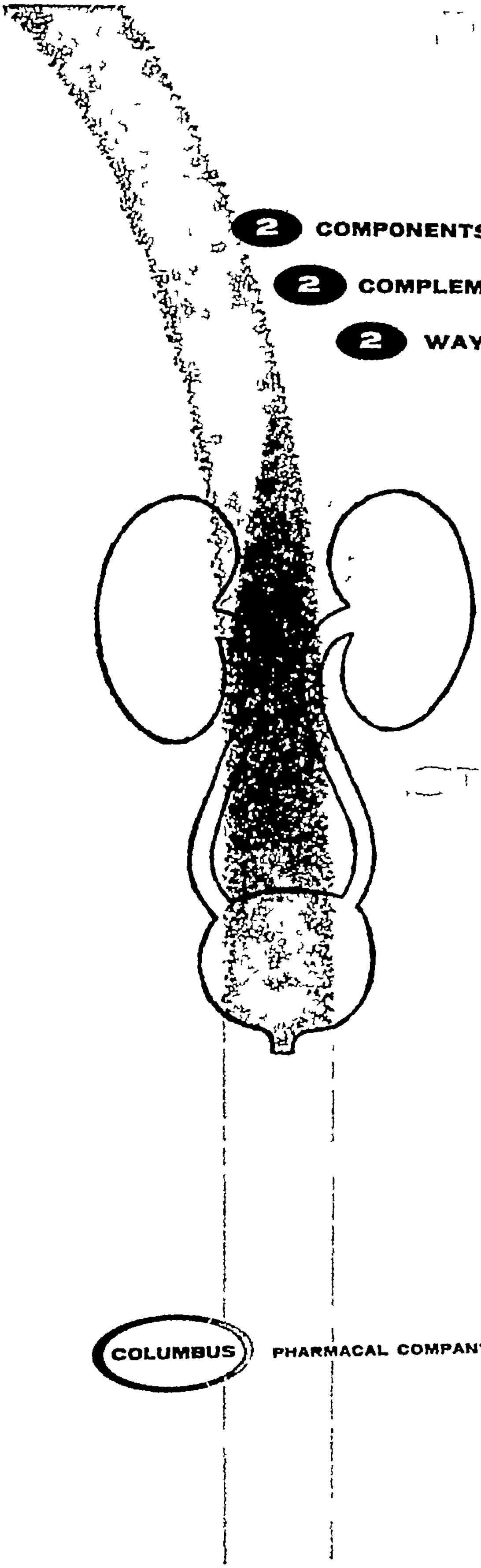

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*H Boyce and F K Garrey* 213
Component of Urinary Cal 228
231
*ch and Eduard Uhlenhuth* 244
ler *J J Cordonnier and W B* 256
*ers C Van Z Hawn and R D* 263
onic Urinary Tract Disease in 270
Disease *R F Norris, V E* 276
nts Treated by Radical Surgery 287
*iam Seltzer and M J Pickett* 292
296
*Hatch* 300

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## CONTENTS

Amount and Nature of Organic Matrix in Calculi *W H Boyce and F K Garvey* 213

Magnesium Dibasic Phosphate Identified as Crystalline Component of Urinary Calculus *Jonathan Parsons* 228

Large Benign Renal Tumors *D G Foster* 231

The Pelvic Ureter in Male and Female *G E Wadsworth and Eduard Uhlenhuth* 244

Betatron Therapy in Advanced Carcinoma of Bladder *J J Cordonnier and W B Seaman* 250

Sarcoma and Carcinoma in Same Bladder *J H Powers C Van Z Hawn and R D Carter* 263

Relationship Between Urethral Resistance and Chronic Urinary Tract Disease in Women. *D M Davis* 270

Resemblance of Prostatic Hypertrophy to Polycystic Disease *R F Norris V E Martens and R W O Gara* 276

Prostatic Carcinoma. Five year Followup of Patients Treated by Radical Surgery *J C Kimbrough* 287

Rapid Speciation of Genus Proteus *R E Hoyt Miriam Seltzer and M J Pickett* 292

Air Cystomanometer *Hossein Golji* 296

Self Sealing Modification of Foley Catheter *J A Hutch* 300

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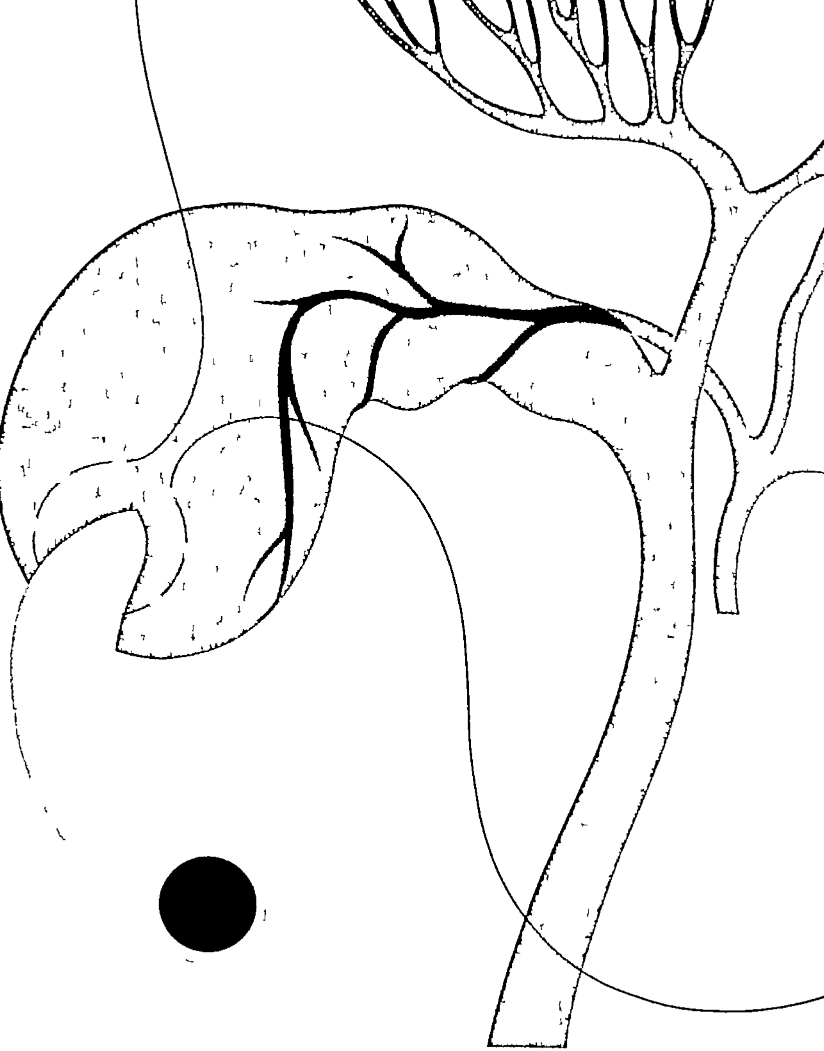

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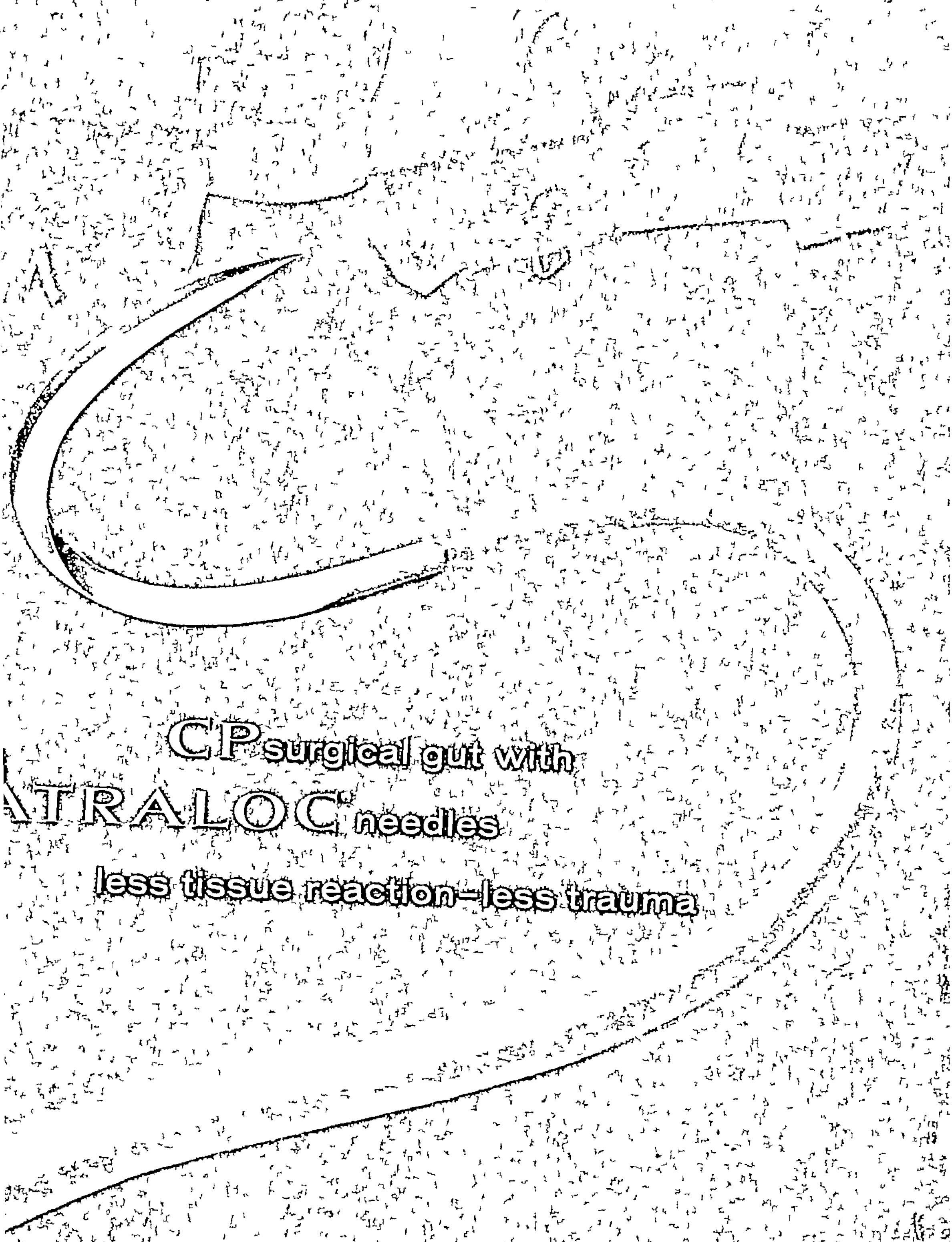
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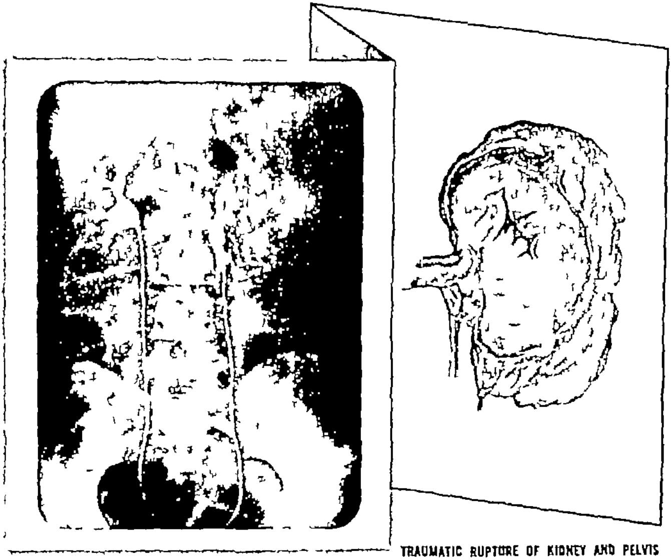

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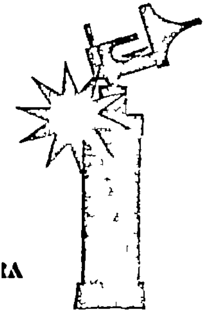

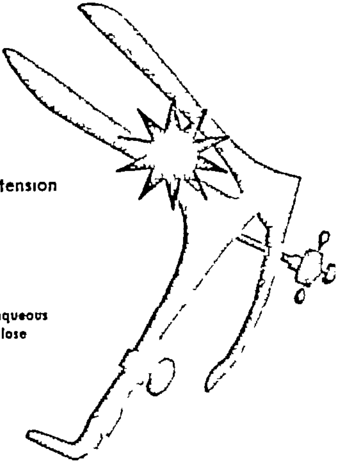

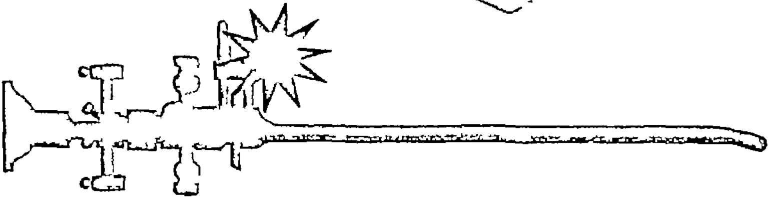

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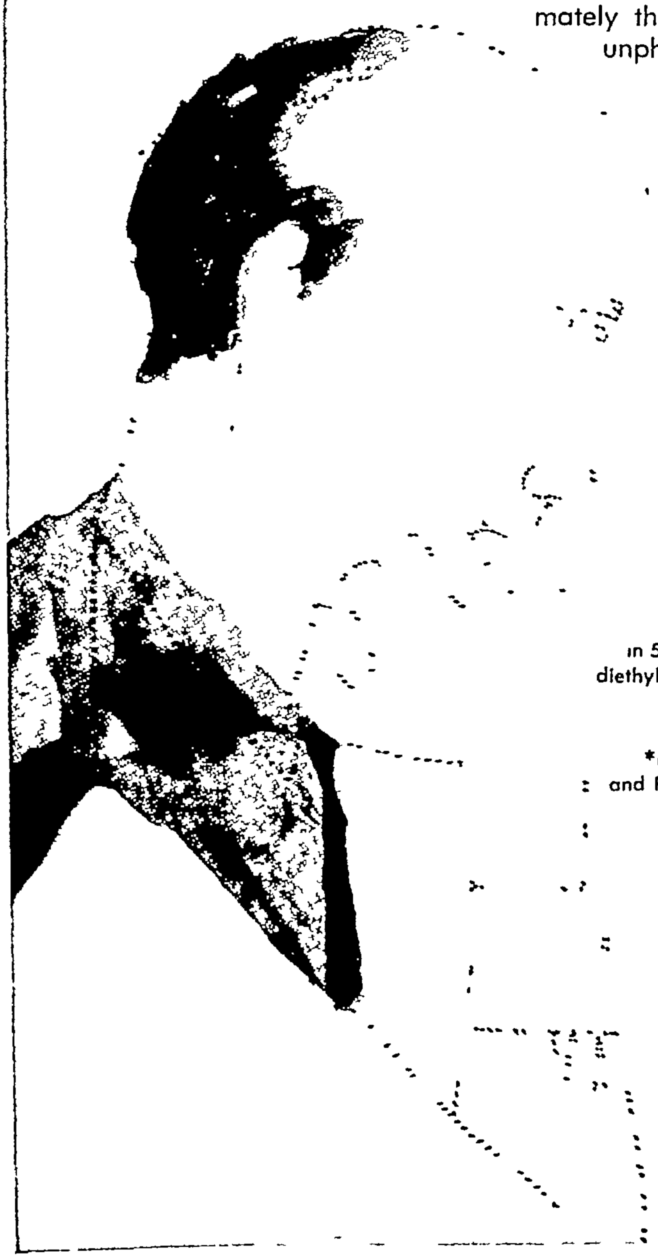

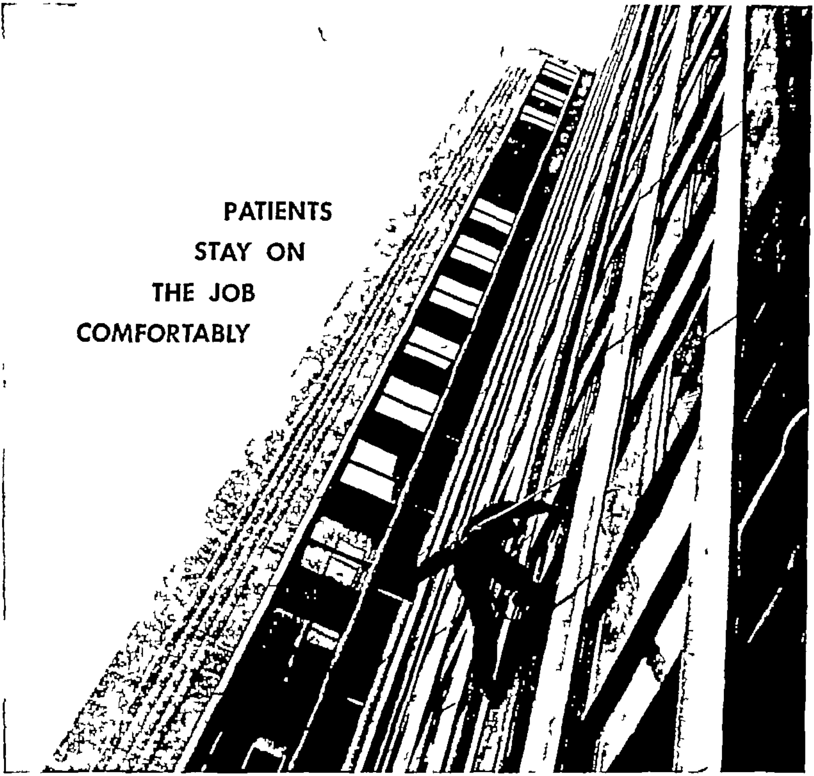

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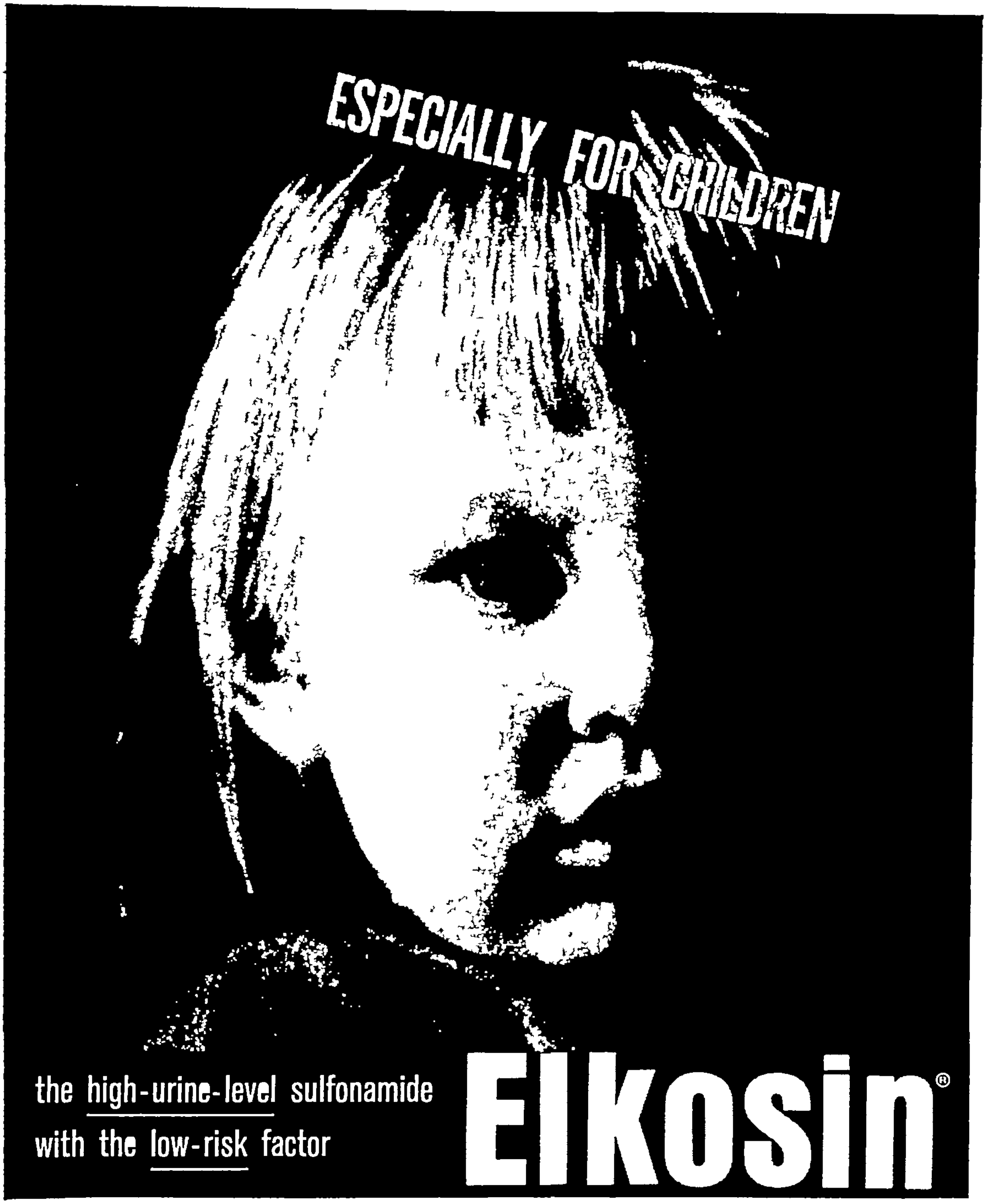

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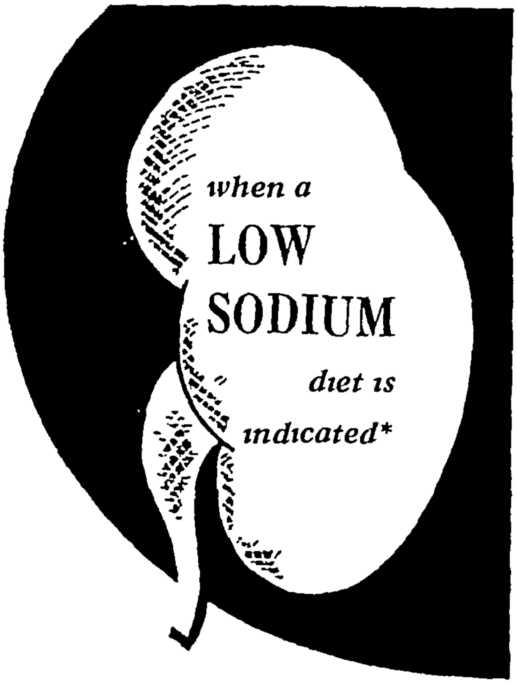

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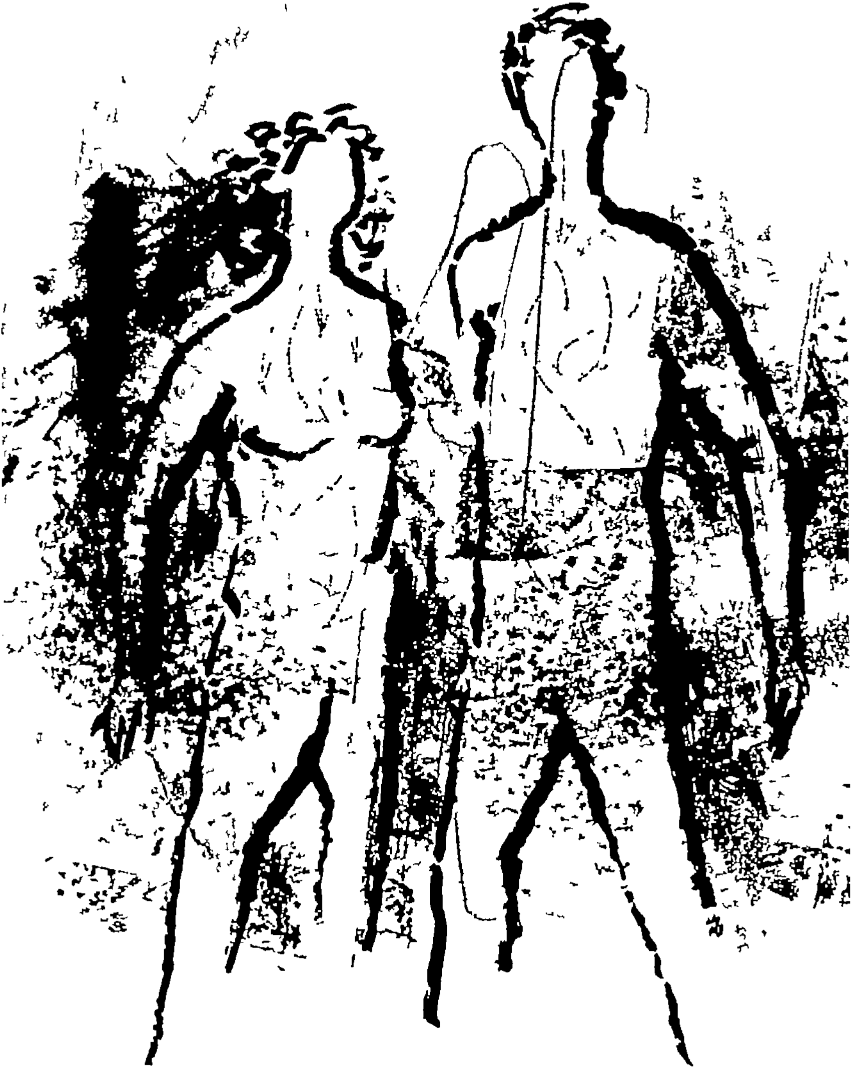

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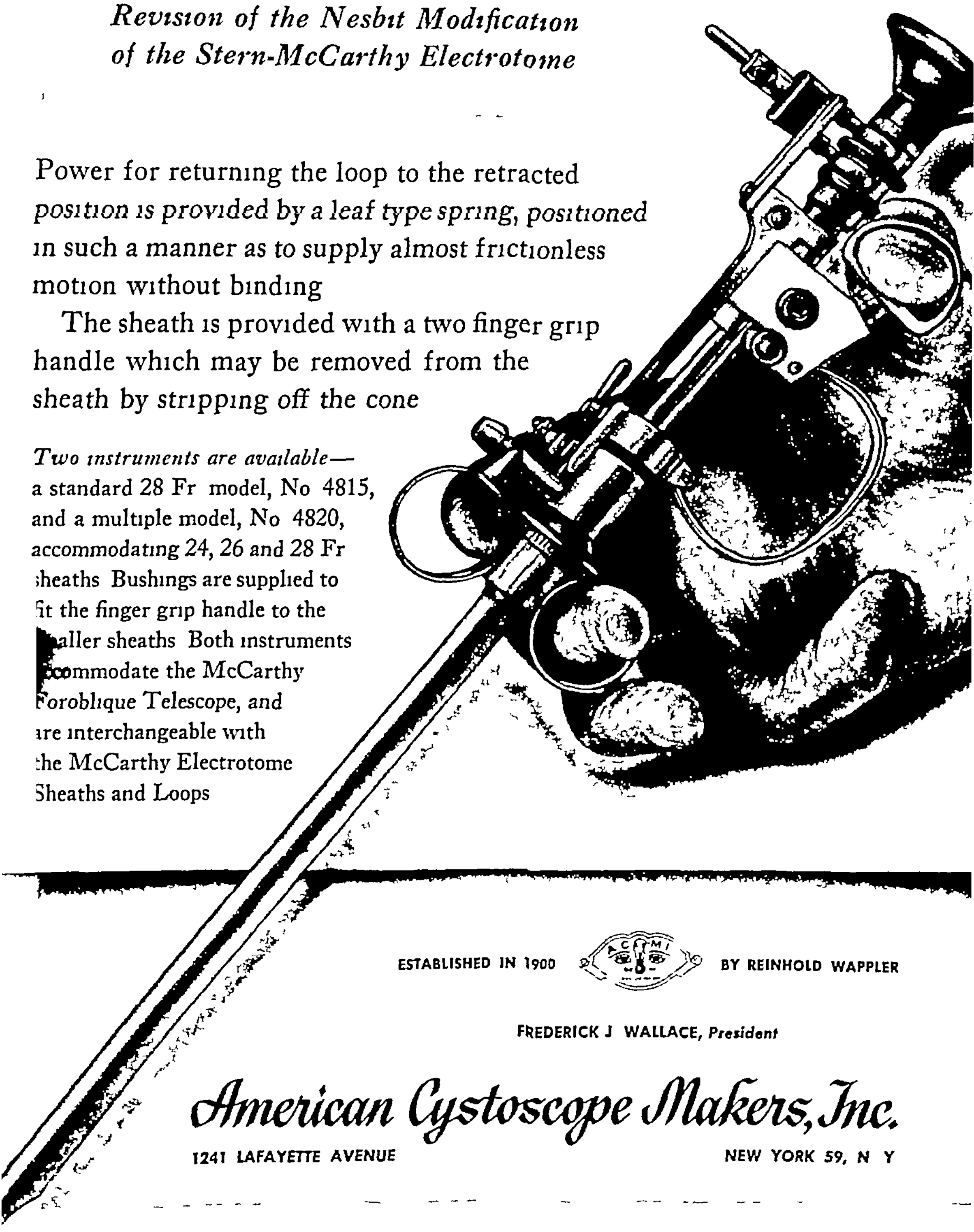

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The Journal of Urology
Vol 76, No 3, September 1956
*Printed in U.S.A*

# THE AMOUNT AND NATURE OF THE ORGANIC MATRIX IN URINARY CALCULI A REVIEW

WILLIAM H BOYCE AND FRED K GARVEY

*From the Department of Urology The Bowman Gray School of Medicine of Wake Forest College Winston-Salem N C*

Stephane Leduc suggested the concept of "osmotic growth" as the mechanism whereby organic bodies are formed in colloidal solutions Mixed colloidal and crystalloidal solutions are never homogeneous but are subject to differentials in osmotic pressure which cause the solutes to move to areas of low osmotic pressure and the solvent to move to areas of high osmotic pressure The hypertonic areas are thus dynamic centers, each with its field of centrifugal and centripetal forces If cohesion of organic molecules intervenes in such centers a true cell is formed the future development of which is influenced by agglutination, precipitation and osmosis—a process which Leduc termed "glomerulisation " The development of equipotential lines in these fields of force results in Liesegang layers and stratification of the organic body The growth, development and evolution of an organic body (calculous matrix) in such osmotic systems (urine) has a duration that constitutes a "life cycle "[1]

Thus did Leduc describe the experiments in his laboratory at Nantes and although his terminology was incomplete by modern standards he provided the background for Lichtwitz's theory of the formation of concretions[2] This theory holds that all concretions depend on 1) the initial formation of an organic structure or matrix, and 2) the subsequent deposition of crystals Lichtwitz accepted the Liesegang ring phenomenon as the cause of concentric laminations in calculi He disagreed with Schade's statement[3] that the concentric architecture is brought about by the alternate deposition of colloid and crystalloid "There is no evidence and little probability that concretions are made like a layer cake "

The present review is based on a series of investigations[4-11] which substantiate

---

This investigation was supported by research grant A 259 from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health Department of Health Education and Welfare, and by a grant in aid from The Squibb Institute for Medical Research New Brunswick, New Jersey

Read at annual meeting of American Urological Association Boston Mass May 30 1956

[1] Leduc Stephane Solutions and Life *in* Colloid Chemistry Jerome Alexander *ed* New York, Chemical Catalog Co Inc vol 2 pp 59–79, 1928

[2] Lichtwitz L The Formation of Concretions *in* Colloid Chemistry Jerome Alexander *ed*, New York Reinhold Publ Corp, vol 5 pp 1063–1082 1944

[3] Schade, H Concretions *in* Colloid Chemistry Jerome Alexander *ed* New York Chemical Catalog Co Inc vol 2 pp 803–844 1928

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[5] Boyce W H Garvey F K and Norfleet C M Proteins and other biocolloids of urine in health and in calculous disease I Electrophoretic studies at pH 4 5 and 8 6 of those components soluble in molar sodium chloride J Clin Invest, **33** 1287–1297, 1954

[6] Boyce W H Garvey F K and Norfleet C M Ion binding properties of electrophoretically homogeneous mucoproteins of urine in normal subjects and in patients with renal calculous disease J Urol **72** 1019–1031 1954

[7] Boyce W H Garvey F K and Norfleet, C M The metal chelate compounds of urine their relation to the initiation and growth of calculi Am J Med **19** 87–95 1955

TABLE 1 *Lyophilized matrix recovered from calcigerous urinary calculi*

| Type of Calculi | Dry Stone Wt. | Matrix Wt | Inorganic Ash | Ash Free Matrix in Stones |
|---|---|---|---|---|
| | *gm* | *gm* | % | % |
| Pool #1 100 stones mixed Ca-Ox 1 $Ca_x(PO_4)_y$ | 68 45 | 2 2041 | 12 46 | 2 82 |
| Pool #2 50 stones $Ca_x(PO_4)_Y$ | 40 24 | 1 0001 | 6 84 | 2 32 |
| Pool #3 25 stones $Ca_x(PO_4)_Y$ $Mg\text{-}NH_4$ $PO_4$ | 35 84 | 0 7526 | 5 22 | 2 00 |
| Pool #4 88 stones Ca-Ox | 35 19 | 1 3358 | 14 98 | 3 22 |
| Pool #5 single staghorn | 25 23 | 0 5940 | 5 37 | 2 23 |
| Total | 204 95 | 5 8866 | 8 97 | 2 52 |

Calculi with as much as 95 per cent of one type crystalline structure are classified as "pure" Matrix wt was determined from material as recovered by ultrafiltration from calculi dissolved in EDTA This treatment (pH 7 8) was never successful in removing all calcium from the matrix The column "inorganic ash" is an expression of residual inorganic material in matrix as recovered from the EDTA solution

and enlarge the general principles of concrement formation as proposed by Leduc and Lichtwitz

## PHYSICAL CHARACTERISTICS OF CALCULOUS MATRIX

*Quantitative studies* Calcigerous calculi have been decalcified in solutions of ethylenediaminetetraacetate, and the matrices recovered by ultrafiltration The average matrix content of 264 calculi so treated was 2 5 per cent by weight, the range among different types of stones being 2 0 to 3 2 gm of matrix per 100 gm of dehydrated calculus (table 1) The matrix content was more closely related to the size of the calculus than to the inorganic crystalline composition Each calculus contains a surface layer of organic matrix, and thus a pool of small calculi presents a much greater surface area and relatively more surface matrix than does a single large calculus The volume of lyophilized matrix obtained from a single calculus is approximately equal to the volume of the original calculus (fig 1)

*Microscopic studies* The matrices have been recovered intact from 117 calculi by fixing the specimens in formalin immediately after operative removal from the urinary tract Calcigerous calculi were than decalcified in ethylenediaminetetraacetate containing 10 per cent formalin Uric acid and cystine calculi were decrystallized in veronal buffer of pH 8 6[12] containing 10 per cent formalin In

---

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[9] Boyce W H and Sulkin, N M The mucopolysaccharide mucoprotein matrix of urinary calculi, biochemical analysis and histochemical studies Proc South Soc Clin Research, Jan 18, 1956 (in press)

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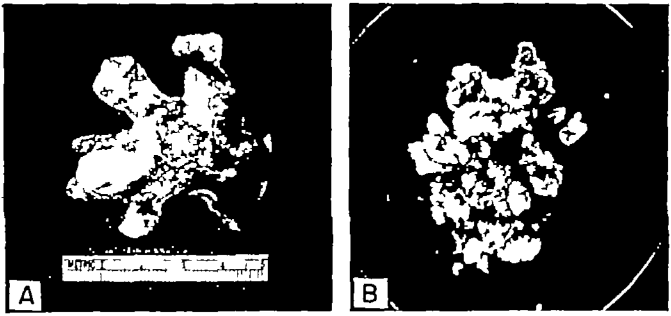

FIG 1 Staghorn calculus and amount of matrix recovered from it Calculus (*A*) was desiccated *in vacuo* to constant weight of 25 23 gm, decrystallized in EDTA and matrix recovered by ultrafiltration Lyophilized matrix (*B*) weighed 0 5621 gm (ash free) and formed 2 23 per cent by weight of calculus In volume it closely approximated that of original calculus

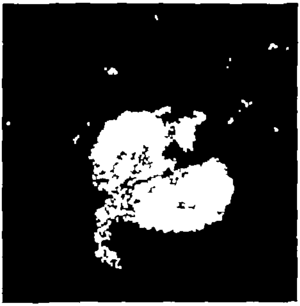

FIG 2 Intact matrix of bisected calculus Calcium oxalate and calcium phosphate calculus fixed in formalin and decrystallized in EDTA Matrix forms a perfect cast of original calculus (Photographed under water)

every instance the matrix formed a perfect cast of the calculus (fig 2) The matrices from cystine calculi could be partially dispersed by agitation but many calcigerous and uric acid calculi had such cohesive matrices that no evidence of decrystallization was apparent until the entire "stone" floated to the surface of the solution

Concentric laminations were clearly visible in the cross-sections of matrices from completely decrystallized calculi Microscopic sections revealed the matrix to be composed of fibrils and an amorphous interfibrillar material (fig 3) The fibrils exhibited parallel orientation of their long axes, and were arranged in broad bands or circular whorls of varying size The central "core" of every calculus was composed of one or more dense, circular whorls of parallel fibers and the accompanying amorphous material (fig 4) In no instance was there a "nidus" of cellular elements or other foreign material

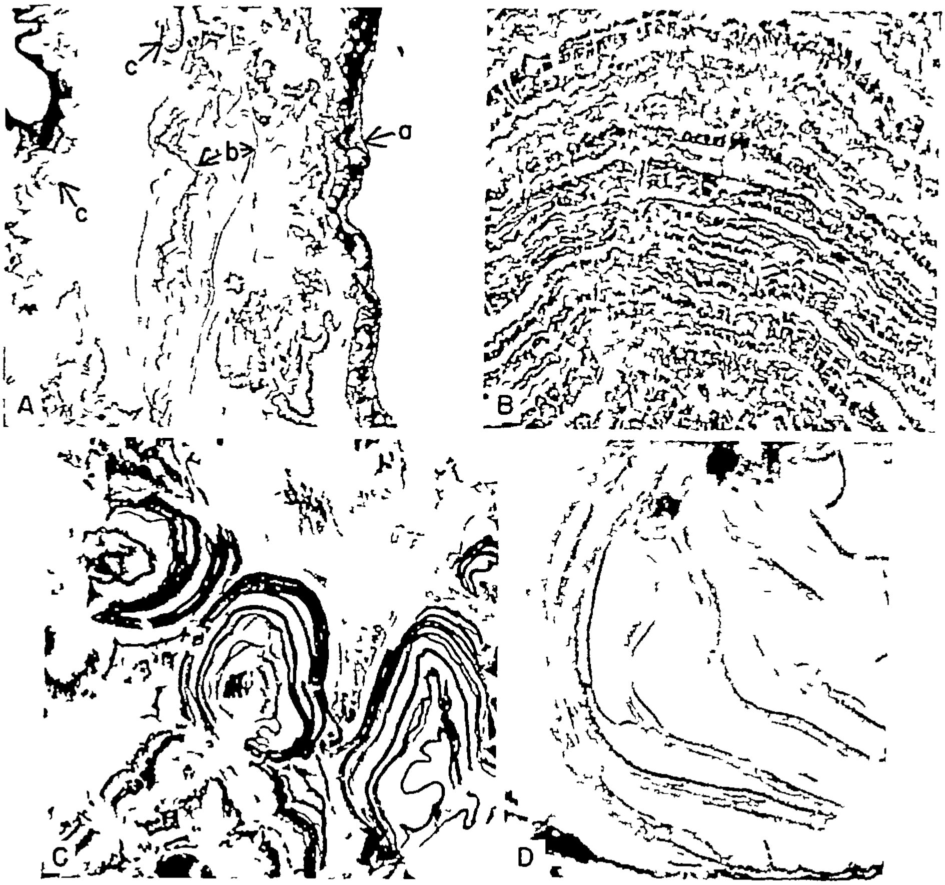

FIG 3 Microscopic appearance of matrix from decrystallized calculi

*A*, calcium phosphate calculus, PAS study with Weigert's counter-stain, magnification ×100 Dense layer of surface material "a", parallel fibrils "b", amorphous interfibrillar material, and several small whorls of matrix "c" are characteristics common to matrices from all calculi

*B*, pure uric acid calculus, PAS study, magnification ×150 Concentric laminations, fibrils, and amorphous interfibrillar material are evident

*C*, center of mixed calcium oxalate and phosphate calculus illustrated in fig 2, PAS stain, magnification ×150 Multiple matrix whorls are common near center of calcigerous calculi

*D*, center of pure calcium phosphate calculus, toluidine blue stain, magnification ×490 Decalcified matrix is largely orthrochromatic but areas of metachromasia are present in all calcigerous calculi

*Relationship of crystalline components to matrix* Microscopic sections of partially decalcified calculi revealed the crystals to be closely aligned with the margins of the fibrils and embedded in the amorphous interfibrillar material (fig 5)

Six patients who had formed calcium phosphate calculi before being placed on a regimen of low calcium intake[13] were subsequently found to have formed roentgenolucent concretions within the renal pelves (figs 6 and 7) The 24-hour

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[13] Garvey, F K and Boyce, W H Diagnostic and therapeutic problems incident to the surgical treatment of "malignant" renal calculous disease J Inter Coll Surg, 25: 310–326, 1956

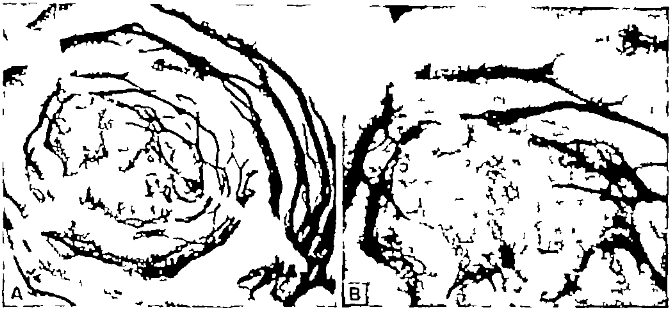

FIG. 4. Central core of pure calcium phosphate calculus which contained a single whorl of matrix. *A*, toluidine blue stain, magnification ×570. *B*, toluidine blue stain, magnification ×1352.

urinary calcium excretion of each patient was less than 36 mg. on three or more determinations, hence these concretions were considered to represent uncrystallized matrix. Upon operative removal, the gross appearance of these concretions was consistent with that of "urostealiths" but they contained no lipids. The inorganic ash content varied between 28 and 46 per cent (dry weight), largely calcium and phosphate—with lesser quantities of sulfate and traces of other elements. Chemical analyses and histochemical studies indicated that the organic components were closely related, if not identical, to matrix recovered from decalcified calculi. Concentric laminations were clearly evident in these uncalcified matrices (fig. 8).

### CHEMICAL COMPOSITION OF CALCULOUS MATRIX

*Elemental composition.* The elemental analysis of matrix from calcigerous calculi has been strikingly constant, regardless of the crystalline composition of the stone. While no significant differences have been detected between the amorphous interfibrillar material and the fibrous components of the matrix, wide variations in carbohydrate and amino acid content may occur within the bounds of this elemental framework (table 2).

*Carbohydrate content.* Both hexose and hexosamine are prominent constituents of calculous matrix, accounting for approximately one third of the weight of the total. No hexuronic acids or 'sialic acid' has been demonstrated in matrix from calcigerous calculi. The principal carbohydrates are galactose and N-acetyl hexosamine (glucosamine?) which occur in approximately equimolar concentration.

*Protein content.* Protein composes approximately two-thirds of the matrix from decalcified calculi. The principal amino acids are threonine and leucine, serine, glycine, tyrosine, arginine and lysine are present in lesser concentrations. There are other constituents which have not been identified but the amino acid "spectrum" of calculous matrix is clearly not consistent with that of collagen

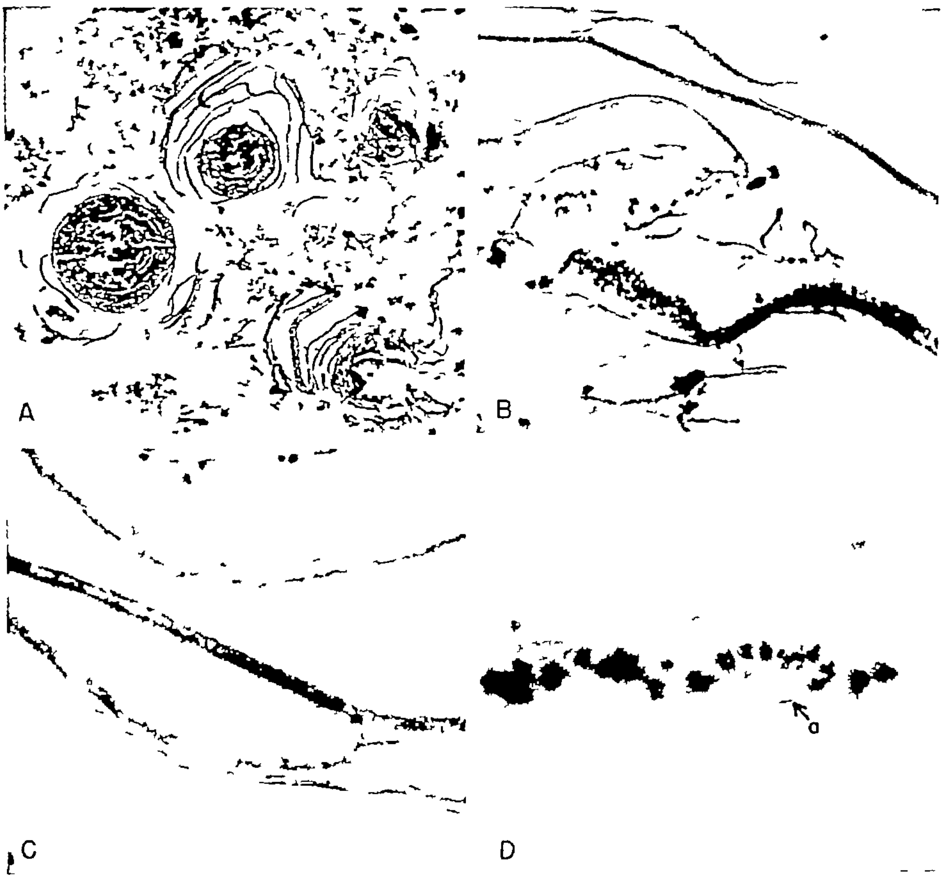

FIG 5 Microscopic appearance of partially decrystallized calculi Von Kossa stain for inorganic crystals (black) and PAS counter-stain for matrix (red)

A, calcium oxalate and phosphate calculus, magnification ×142 Even with much residual inorganic crystals alignment of crystals on matrix fibrils is clearly illustrated

*B*, calcium phosphate calculus, magnification ×570

*C*, calcium oxalate calculus with less than 5 per cent phosphate, magnification ×1352 Note small residual crystals along margin of fibrils

*D*, calcium phosphate calculus, magnification ×1352 Crystals are present in large groups and smaller units "a" They are aligned with fibrils and embeded in amorphous interfibrillar material

## HISTOCHEMICAL CHARACTERISTICS OF CALCULOUS MATRIX

*Periodic acid Schiff leucofuchsin reaction* Both the fibrillar and the amorphous forms of the matrix gave a positive reaction to this test This finding is considered to demonstrate the presence of a mucoprotein, since glycogen was eliminated by treatment with diastase prior to the PAS treatment, and the presence of partially oxidized lipids was excluded by negative *Sudan black* studies of comparable material

*Aqueous toluidine blue* The greater portion of *de*calcified matrix gives a diffuse blue reaction (orthochromasia) with this test, but areas of distinct purplish-red metachromasia were observed in all matrices studied by serial section The *un*calcified matrix gave a brilliant generalized metachromasia with this test (fig 8)

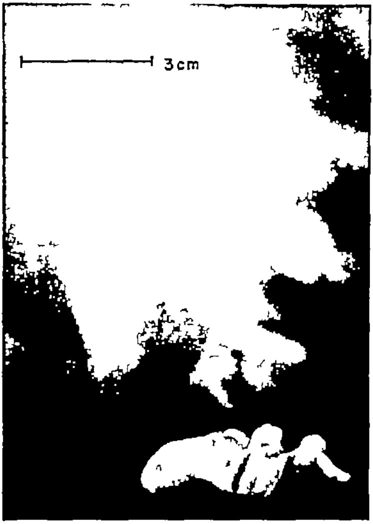

FIG 6 Uncalcified matrix (organic concretion) Roentgenolucent mass filling lowest calyces and extending into pelvis formed after removal of a calcium phosphate calculus by pyelolithotomy Urinary calcium excretion was less than 30 mg /24 hr on a low calcium low vitamin D high phytate regimen There was no infection of urinary tract

Specimen (insert) had appearance of 'urostealith' but contained no lipid Organic components were mucoprotein mucopolysaccharide of same composition as matrix from decalcified calculi Inorganic ash (calcium phosphate) accounted for 46 per cent by weight of specimen but no crystals were detected on microscopic examination

The presence of a mucopolysaccharide containing ester sulfate is suggested by the metachromasia, by a sulfate content of 9 to 14 per cent of the carbohydrate components, and by the retention of a net negative charge at pH 3.2

### POSSIBLE SOURCES OF CALCULOUS MATRIX

The organic matrix of decalcified calculi is quite constant in composition Present knowledge would indicate that it is composed of both a mucoprotein (PAS positive) and a sulfated mucopolysaccharide (metachromatic) which are united by such strong chemical bonds that they are difficult to separate without being degraded to the component monosaccharides and amino acids The presence of galactose and hexosamine in equimolar concentrations sufficient to account for practically all of the carbohydrate content, together with the absence of hexuronic acid and "sialic acid", limits the possible precursors of stone matrix to a relatively narrow field

*Mucoproteins and mucopolysaccharides of urine* The constant composition of matrix assumes an etiologic significance when one considers the number of mucopolysaccharides and mucoproteins present in urine

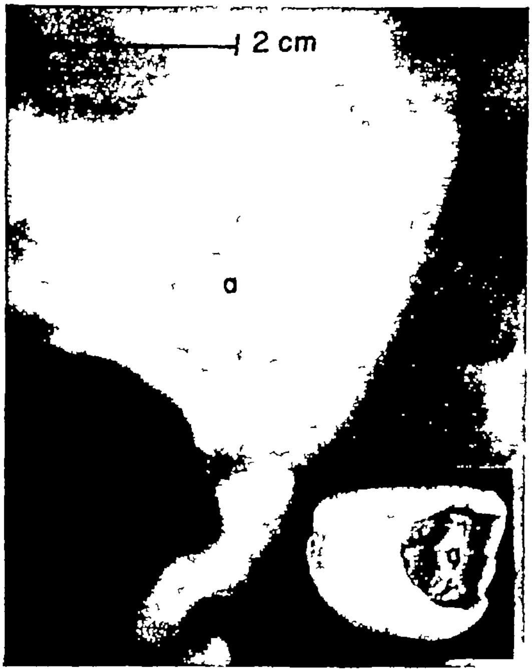

FIG 7 Calcium phosphate calculus with large cover of uncalcified matrix Twenty-four hour urinary calcium excretion was 18 to 35 mg at time of study Concentric laminations of the organic cover and calcified center "a" are illustrated in the sectioned specimen (insert)

Determination of the nondiffusible (bound) hexosamine content of urine has indicated a marked increase in the amount of mucopolysaccharide, mucoprotein, or both found in the urine of patients with renal calculous disease, diabetes mellitus, thyrotoxicosis, multiple myeloma, and advanced atherosclerosis [14] Some of these bound amino sugars probably arrive in the urine by glomerular filtration, since a correlation has been established between the amount of protein-bound hexose and hexosamine found in the plasma and that found in the urine of patients with some of the above diseases [15]

Anderson, Lockery and Malaglan[16] have isolated three mucoprotein components from normal urine, one of which is the virus inhibitory mucoprotein of Tamm and Horsfall [17] Neutral mucopolysaccharides analogous to the specific substances found in blood groups A, B, and O have been recovered from normal urine [18] Serum glycoproteins (MP-2) are present in normal urine in relatively

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[14] King, J S and Warnock, N H Some clinical conditions affecting the urinary excretion of non-dialyzable hexosamine Proc Soc Exper Biol & Med (in press)

[15] Hamerman, D , Reife, A and Bartz, K W Levels of hexosamine and hexose in plasma and urine in patients with certain diseases or injuries J Lab & Clin Med (in press)

[16] Anderson, A J , Lockery, E and Maclagan, N F Some biological properties of the urinary mucoproteins Proc Biochem Soc , Biochem J (Lond ), 60 41, 1955

[17] Tamm, I and Porter, Kieth R Direct visualization of a mucoprotein component of urine J Biol Chem , 212 135–140, 1955

[18] Hamerman, D , Reife, A , Bartz, K W and Hatch, F T The nature of high molecular weight carbohydrate-protein constituents in normal human urine Report No 154, Medical Nutrition Lab , Fitzsimons Army Hospital, U S Army, Denver 8, Colorado, Feb 24, 1955

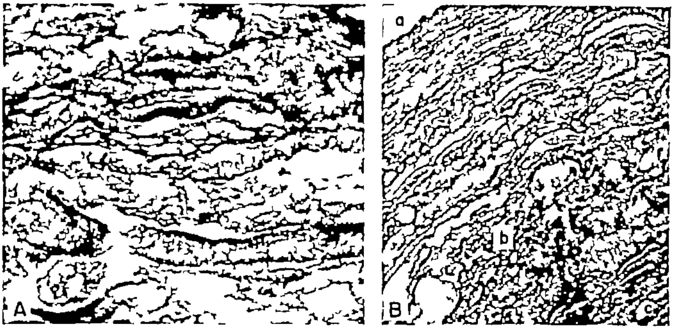

FIG 8 Microscopic appearance of calculus illustrated in fig 7

*A* untreated cover of organic material PAS study magnification ×570 Amorphous interfibrillar material is present in relatively greater amounts than in decalcified matrices

*B*, section of entire specimen after decalcification in EDTA Toluidine blue stain magnification ×100 Surface of specimen a , junction of organic cover and previously calcified center b and decalcified matrix 'c' are illustrated Uncalcified matrix between 'a' and b was highly metachromatic decalcified area c ' was orthochromatic with areas of metachromasia Concentric laminations of uncalcified matrix are clearly evident

large concentration[8] Serum orosomucoid (MP-1) has been demonstrated in the urine of patients with the nephrotic syndrome[19] Gonadotropic hormones are mucoproteins present in the urine in variable concentration[20] Acidic mucopolysaccharides which exhibit metachromasia and contain hexuronic acid have been recovered from human leukocytes and from urine[21] Both chondroitin sulfate[22] and heparin[23] may be present in urine, but neither has been clearly identified

Many pathogenic bacteria produce mucopolysaccharides which are highly metachromatic with aqueous toluidine blue[24] These mucopolysaccharides have not been recovered from urine, but are undoubtedly present in the urine of patients with pyelonephritis due to Bacillus coli Proteus vulgaris, Staphylococcus aureus, and other polysaccharide producing bacteria These (bacterial) mucopolysaccharides are not considered likely sources of calculous matrix since the elemental composition and carbohydrate content of all known bacterial polysaccharides are so markedly different from those of calculous matrix

*Mucopolysaccharides of bone matrix* The frequent coexistence of bone disease and urinary calculi is probably due to dissolution of bone matrix in addition to

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[19] Popenoe, E A Characterization of a glycoprotein in the urine of patients with proteinuria J Biol Chem 217 61–66 1955

[20] Gurin S Bachman D and Wilson D W The gonadotropic hormone of urine of pregnancy II Chemical studies of preparations having high biological activity J Biol Chem 133 467–476 1940

[21] Kerby G P The occurrence of acid mucopolysaccharides in human leukocytes and urine J Clin Invest 34 1738–1743 1955

[22] Kerby G P The excretion of glucuronic acid and of acid mucopolysaccharides in normal human urine J Clin Invest 33 1168–1174 1954

[23] Astrup P On the determination of heparin in blood plasma and urine Acta pharmacol et toxicol 3 165–174 1947

[24] Kent P W and Whitehouse M W Biochemistry of the Aminosugars New York Academic Press Inc p 133 1955

TABLE 2 *Elemental composition of typical mucoids*

| | Nitrogen | Sulfur | Carbon | Hydrogen | Oxygen |
|---|---|---|---|---|---|
| Tendomucoid* | 11 75 | 2 33 | 48 76 | 6 53 | 30 60 |
| Osseomucoid* | 12 22 | 2 32 | 47 43 | 6 63 | 31 40 |
| Uromucoid† | 12 2 | 1 80 | 48 9 | 6 9 | 30 2§ |
| Calculous matrix‡ | 10 43 | 0 85 | 57 55 | 7 21 | 24 0§ |

* Hawk, P B , Oser, B L and Summerson, W H , Practical Physiological Chemistry, 12th ed , New York, Blakiston Co , 1951, p 178

† Boyce, W H and Swanson, M , J Clin Invest , *34* 1581, 1955

‡ Boyce, W H and Sulkin, N M , J Clin Invest , (In press)

§ Calculated

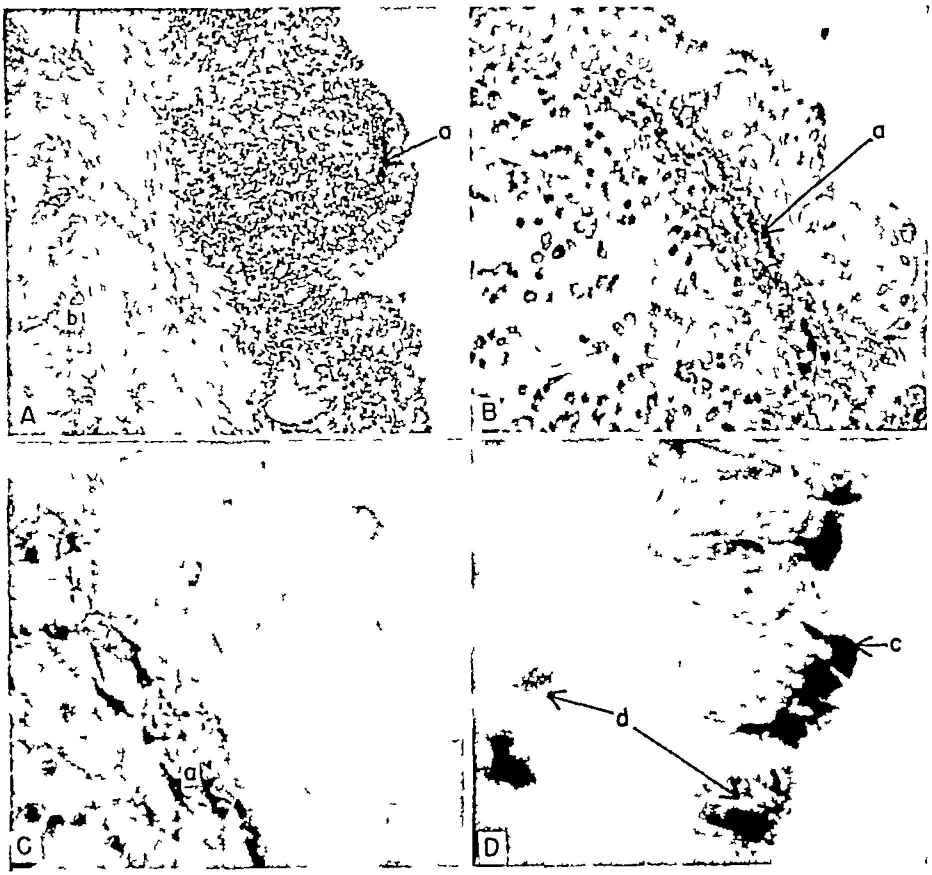

FIG 9 Histochemical studies of renal pelves from patient with recurrent calcium phosphate calculi

*A*, aqueous toluidine blue stain, magnification ×150 Deep purplish red metachromasia of extracellular mucopolysaccharide is collected beneath epithelium at "a" and between muscle bundles at "b"

*B*, same as *A*, magnification ×340

*C*, same as *A*, magnification ×570

*D*, section from same block as *C*, PAS study with Weigert's counter-stain, magnification ×1352 Cytoplasmic granules of mucoprotein "c" give a brilliantly positive PAS test but do not stain with toluidine blue Cell nuclei "d" are stained by Weigert's hematoxylin

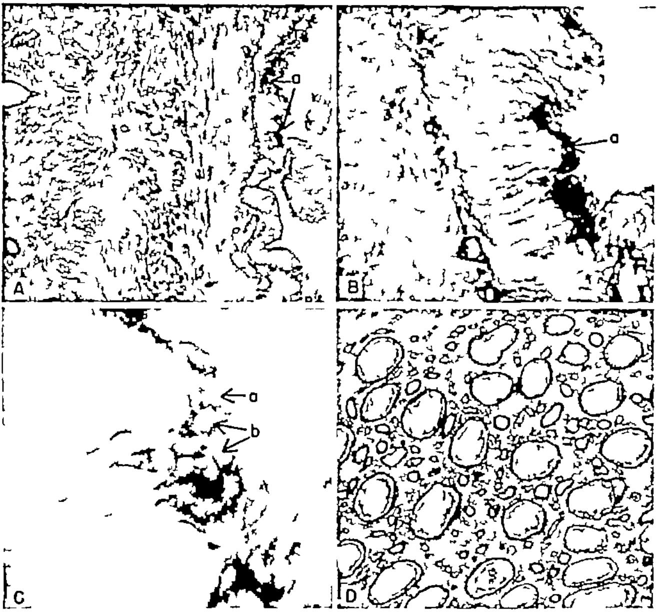

Fig 10 Histochemical studies of renal pelvis from patient with recurrent calcium phosphate calculi

*A*, periodic acid Schiff leucofuchsin study with Weigert's counter-stain magnification ×150 Cytoplasmic granules of PAS positive mucoprotein a' are clearly visible

*B* same as *A* magnification ×570

*C*, PAS study of section comparable to *A* without counterstain magnification ×1352 Cytoplasmic granules a surround unstained nuclei b

*D*, PAS study of renal papilla from same patient, magnification ×150 There is increase in PAS positive material about basement membranes and within stroma as compared with similar studies of normal kidney This is not specific for calculous disease and has been observed in pyelonephritis and in many noninfectious diseases of kidney

the mobilization of inorganic ions [25] [26] A mucopolysaccharide closely related in chemical composition to that of calculous matrix was first recovered from bovine corneas by Karl Meyer and his associates [27] This was designated "keratosulfate", and Meyer has recently reported the recovery of this material from the matrix of growing bone [28]

*Mucopolysaccharides of connective tissue* Two sulfated mucopolysaccharides

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[25] Howard J E Clinical and laboratory research concerning mechanisms of formation and control of calculous disease by the kidney J Urol 72 999-1008, 1954

[26] Engel M B and Catchpole, H R Excretion of urinary mucoprotein following parathyroid extract in rats Proc Soc Exper Biol & Med 84 336-338 1953

[27] Meyer K Linker A Davidson E A and Weissman B The mucopolysaccharides of bovine cornea J Biol Chem 205 611-616 1953

[28] Meyer K Personal communication

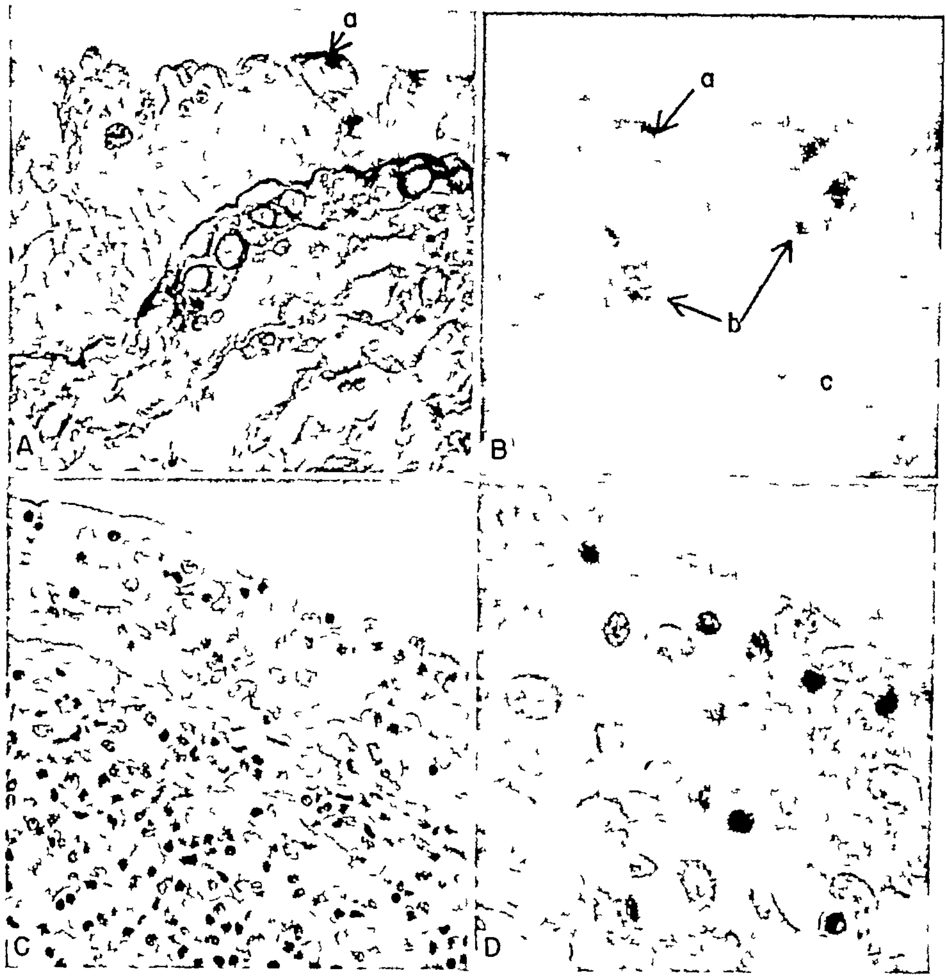

FIG 11 Histochemical studies of renal pelves from patients with congenital hydronephrosis and pyelonephritis

*A*, patient aged 28 years with small phosphatic calculus in renal pelvis PAS study with Weigert's counter stain, magnification ×570 PAS positive cytoplasmic granules "a" are not abundant but are present

*B*, section similar to *A*, PAS study only, magnification ×1352 Cytoplasmic granules are dispersed in cytoplasm "a" and grouped about vacuoles "b" which may represent unstained nuclei "c"

*C*, patient aged 34 years with no urinary calculi PAS study with Weigert's counter stain, magnification ×570 No PAS positive cytoplasmic granules are present All staining is due to Weigert's treatment which is essential for illustration since PAS alone produces insufficient staining for photographic reproduction (Compare with fig 10-*C* )

*D*, same as *C*, magnification ×1352

which are metachromatic and contain no uronic acids have been recovered from human connective tissues by Consden and Bird[29] One of these may be keratosulfate and the other is closely related but contains mannose

A striking metachromasia of the connective tissues of the urinary tract has been found in studies of surgical and autopsy specimens from patients with

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[29] Consden, R and Bird, R The carbohydrate of connective tissues Nature, **173** 996–997, 1954

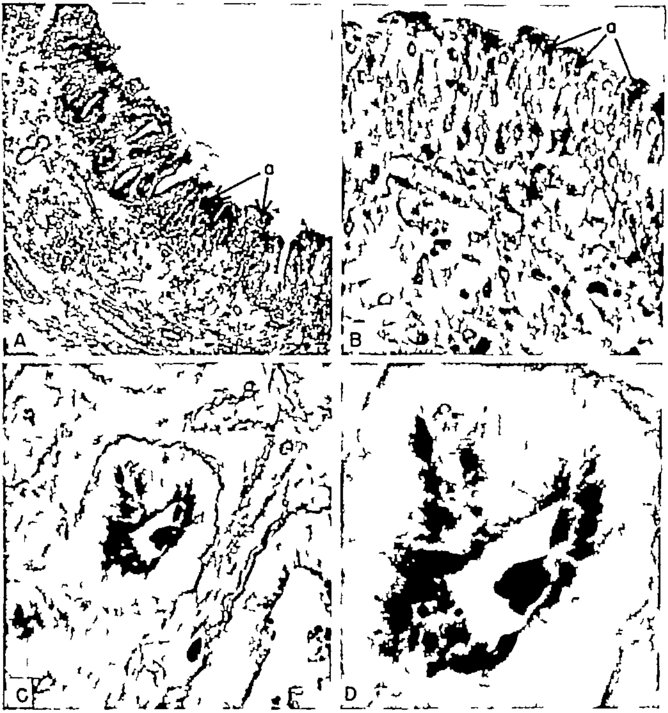

FIG 12 Histochemical studies of bladder epithelium

*A* Exstrophy of bladder PAS study with Weigert's counter-stain magnification ×100 Abundance of PAS positive cytoplasmic granules a is evident

*B* same as A magnification ×570

*C* patient aged 54 years with cystitis glandularis and no calculus formation PAS study without counterstain magnification ×570 Dark red cytoplasmic granules of PAS positive mucoprotein are clearly evident

*D* same as *C* magnification ×1352 Cells filled with PAS positive material appear to be on verge of rupture into lumen of crypt Small cysts (not illustrated) were filled with amorphous PAS positive material and exhibited an atrophic or absent epithelial lining

renal calculi[11] No comparable changes have been noted in similar specimens from normal subjects or from patients with a variety of other urinary diseases The metachromasia with toluidine blue is apparent in the connective tissues of the renal papillae, and within the walls of the renal pelves and ureters Collections of extracellular material which give an intense metachromasia with aqueous toluidine blue are commonly present in the basement membrane of the urinary epithelium (fig 9) This material does not give a positive reaction with the periodic acid Schiff leucofuchsin technique

*Mucoproteins of urinary epithelium* Quantitatively the largest mucoprotein component of normal urine is the virus inhibitory mucoprotein of Tamm and Horsfall, which formed the fraction II or "uromucoid" of previous studies[6] This material is much increased in the urine of patients with calculous disease It is insoluble in concentrated urine and gives a positive PAS reaction, but is not metachromatic with toluidine blue Although it shows little tendency to bind calcium in the native state, it can be converted into an active chelating agent for calcium by mild alkaline hydrolysis[6] It has a molecular weight of seven million and an axial ratio of 1 250, so that the molecules form enormously elongated nodose structures[17] Solutions of this material tend to form gels under certain laboratory conditions[8]

A consistent correlation has been established between the preoperative concentration of T&H mucoprotein in the urine and the presence of PAS positive cytoplasmic granules in the transitional epithelium removed from the urinary tract at operation These cytoplasmic epithelial granules have been consistently present in patients with renal calculi (fig 10) The granules have not been confined to the epithelium immediately adjacent to the calculus, but have been present to a variable degree in the ureteral and vesical epithelium Furthermore, they have been absent from the epithelium of several patients with longstanding obstructive hydronephrosis and chronic pyelonephritis who did not form calculi (fig 11) On the other hand, these PAS positive cytoplasmic granules have been present in some patients, including those with cystitis glandularis and exstrophy of the bladder, who formed no calculi (fig 12) It has been previously suggested that T&H mucoprotein is a secretory product of the transitional epithelium,[8, 17] and the present studies are in accord with this assumption

In spite of the obvious implications, there is no conclusive evidence that T&H mucoprotein forms any significant part of calculous matrix T&H mucoprotein contains "sialic acid," mannose, and fucose, none of which have been demonstrable in calculous matrix The T&H mucoprotein recovered from the urine of patients with calculous disease is not structurally different from that in the urine of normal subjects[8] Although alkaline or acid hydrolysis alters the carbohydrate content of this material, both hexosamine and "sialic acid" are among the more labile components At present the increase of T&H mucoprotein in the urine of patients with calculous disease must be considered a secondary phenomenon resulting from mechanical or bacterial stimulation of the transitional epithelium, rather than a primary factor in the formation of calculous matrix

## SUMMARY

The initial and essential phase in calculous formation is believed to be a condensation of specific organic molecules within the collecting system of the urinary tract Present knowledge indicates that these molecules are both mucopolysaccharide and mucoprotein united by strong chemical bonds The initial coagulum of uncalcified matrix may vary in size from a few molecules which

form a "micelle" to a mass large enough to fill a renal calyx or pelvis The tendency of this framework to form spherules may result in "multinucleated" calculi and asymmetrical stones The subsequent growth of a formed calculus is dependent upon the deposition of additional matrix, either as broad layers over the entire stone or as localized surface deposits producing asymmetric enlargement and moulding The formation of separate coagula accounts for the production of secondary calculi without additional increase in the size of calculi already present in the same renal pelvis

Deposition of inorganic crystals is a secondary phenomenon which usually occurs quite rapidly, but it may require weeks to reach a maximum density in large calculi The deposition of crystals is governed by those principles of physical chemistry which control the formation of crystals from complex solutions Failure of the matrix to undergo calcification results in radiolucent bodies sometimes erroneously regarded as "urostealiths' This failure may be due to alterations either in the ion binding properties of the matrix or in the composition of the urine The free diffusion of solutes into the matrix mass may be an influential factor in crystal deposition

The origin of calculous matrix remains unknown The demonstration of keratosulfate in bone matrix and in the cornea, and the presence of a closely similar or identical mucopolysaccharide in connective tissue and in calculous matrix suggest that keratosulfate may be the essential substrate for calcification If such proves to be the case, then the mucopolysaccharide (metachromatic) *component of calculi may be derived from bone matrix and connective tissues* far distant from the urinary tract, or may be derived from the connective tissues of the urinary tract itself under the influence of local diseases The origin of the mucoprotein (PAS positive) component of calculous matrix is even more obscure It may be derived from the transitional epithelium, but, if so, it is markedly different from the normal secretory product of these cells

The following conclusions seem to be justified by the cumulative data now in hand 1) The number, size, shape, color, and concentric laminations of calculi are determined solely by the organic matrix 2) Concretions composed of this organic matrix and a minimum of inorganic salts may occur without crystal formation but no crystalline concretion can develop in the absence of the organic matrix

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# MAGNESIUM DIBASIC PHOSPHATE IDENTIFIED AS A CRYSTALLINE COMPONENT OF A URINARY CALCULUS

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Magnesium ammonium phosphate hexahydrate ($MgNH_4PO_4\ 6H_2O$) is found as a constituent of urinary calculi[1] being commonly associated with alkaline infected urine This crystalline material often occurs mixed with one of several complex calcium phosphate compounds commonly called by the general name apatite It is the purpose of this paper to report the identification of a new magnesium phosphate calculus constituent

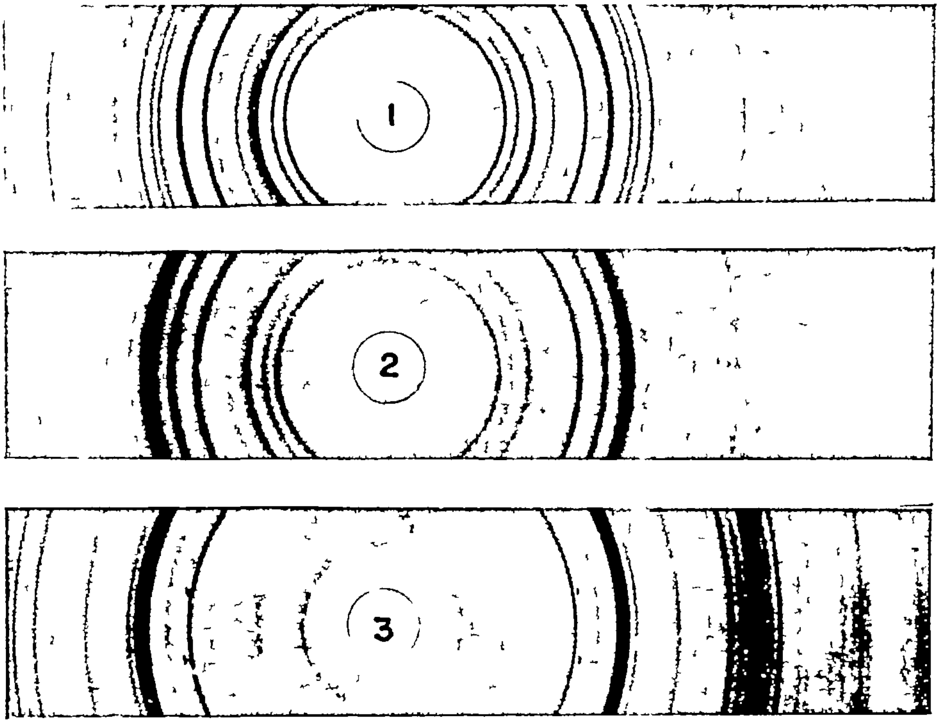

FIG 1 X-ray diffraction powder patterns *1*, Magnesium dibasic phosphate trihydrate standard, *2*, calculus, *3*, hydroxyl apatite standard

During the routine analysis of urinary calculi by x-ray diffraction carried on in the Physics Department of this Institute A crystalline component previously unreported has been found The compound occurring as a major constituent has been identified as the trihydrate of magnesium dibasic phosphate ($MgHPO_4\ 3H_2O$) This kidney stone was composed of a combination of the above compound and hydroxyl apatite

When this pattern was first studied a tentative analysis was made from one of

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[1] Prien, E L and Frondel, C J Urol , 57 970, 1947

TABLE 1 *Comparison of x ray diffraction powder pattern interplanar spacings*

| Calculus | | Standard $MgHPO_4$ $3H_2O$ | | Standard Apatite | |
|---|---|---|---|---|---|
| d* | $I/I_1$† | d | $I/I_1$ | d | $I/I_1$ |
| | | | | 8 23 | 0 24 |
| 5 89 | 0 27 | 5 95 | 0 49 | | |
| 5 33 | 0 20 | 5 35 | 0 36 | 5 31 | 0 10 |
| 4 73 | 0 36 | 4 73 | 0 49 | | |
| 4 56 | 0 13 | 4 49 | 0 20 | 4 50 | 0 02 |
| 4 15 | 0 20 | 4 14 | 0 27 | 4 08 | 0 04 |
| | | | | 3 88 | 0 18 |
| 3 68 | 0 09 | 3 68 | 0 20 | 3 66 | 0 04 |
| 3 45 | 0 67 | 3 47 | 1 00 | 3 45 | 0 60 |
| 3 13 | 0 02 | 3 20 | 0 13 | 3 18 | 0 12 |
| 3 05 | 0 58 | 3 07 | 0 67 | 3 09 | 0 32 |
| 2 81 | 1 00 | 2 81 | 0 36 | 2 81 | 1 00 |
| 2 73 | 0 49 | 2 73 | 0 36 | 2 74 | 0 70 |
| | | | | 2 65 | 0 40 |
| 2 59 | 0 49 | 2 59 | 0 36 | | |
| 2 51 | 0 02 | 2 53 | 0 09 | 2 54 | 0 02 |
| 2 40 | 0 13 | 2 38 | 0 20 | | |
| 2 29 | 0 09 | | | 2 27 | 0 40 |
| 2 20 | 0 13 | 2 21 | 0 20 | | |
| | | 2 14 | 0 09 | 2 15 | 0 08 |
| 2 08 | 0 13 | 2 09 | 0 13 | 2 07 | 0 08 |
| 2 03 | 0 13 | 2 04 | 0 13 | | |
| | | | | 2 00 | 0 06 |
| 1 97 | 0 04 | 1 98 | 0 13 | | |
| 1 94 | 0 20 | 1 93 | 0 27 | 1 95 | 0 44 |
| 1 89 | 0 09 | 1 89 | 0 09 | 1 89 | 0 18 |
| | | | | 1 84 | 0 50 |
| | | | | 1 82 | 0 12 |
| 1 79 | 0 09 | 1 80 | 0 09 | 1 78 | 0 08 |
| 1 76 | 0 13 | 1 76 | 0 13 | 1 76 | 0 12 |
| 1 73 | 0 13 | 1 72 | 0 04 | 1 72 | 0 32 |
| 1 68 | 0 13 | 1 68 | 0 09 | 1 65 | 0 12 |
| 1 60 | 0 20 | 1 60 | 0 13 | 1 61 | 0 04 |
| 1 56 | 0 04 | 1 57 | 0 09 | 1 58 | 0 02 |
| 1 50 | 0 06 | 1 49 | 0 04 | 1 51 | 0 12 |
| | | 1 47 | 0 04 | 1 48 | 0 12 |
| 1 44 | 0 09 | 1 45 | 0 04 | 1 45 | 0 24 |
| | | | | 1 44 | 0 12 |
| 1 41 | 0 09 | 1 42 | 0 13 | | |
| 1 38 | 0 04 | 1 39 | 0 13 | 1 35 | 0 02 |

* Values in Angstrom units

† Relative intensities by calibration strip comparison

the ASTM powder data cards[2] A new standard pattern was then run from chemically pure magnesium dibasic phosphate obtained from a laboratory supply house The latter pattern was compared with the calculus pattern and close agreement noted In Figure 1 the calculus pattern is shown between the magnesium dibasic phosphate standard pattern (above) and hydroxyl apatite (below) The strong apatite line can be seen superimposed upon a pattern closely matching that of the magnesium dibasic phosphate standard Table 1 shows the interplanar spacing data as compared with the same data from the standard compounds An emission spectrographic analysis* made from this same calculus powder confirmed that magnesium, phosphorus, and calcium were the elements present in major proportions

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[2] X ray diffraction data cards Published by The American Society for Testing Materials (1946–1955) 1916 Race Street Philadelphia 3 Pa

The following x-ray diffraction procedures were used The specimens were powdered to about 200-mesh size and mounted in thin walled plastic tubes These tubes have a wall thickness of 0 01 mm and an inside diameter of 0 2 mm The mounted samples were exposed for 3 hours in Norelco (North American Philips Co , Inc ) 114 59 mm diameter, Debye Scherrer cameras Eastman no-screen x-ray film was used Nickel-filtered copper radiation produced at 35 KVP and 20 ma current was employed

* This analysis was made through the courtesy of the Research Laboratories Division, General Motors Corporation

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# LARGE BENIGN RENAL TUMORS A REVIEW OF THE LITERATURE AND REPORT OF A CASE IN CHILDHOOD

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Malignant tumors of the kidney are quite common, comprising about two per cent of all tumors in adults and about twenty per cent of those in children (Harvey) Benign renal tumors, however, are so rare that many standard pathology textbooks as well as articles on renal tumors in the literature fail to even mention them Benign tumors of the kidney which have been reported in the literature from time to time are the adenoma, angioma, fibroma, lipoma, myoma and a mixed group made up of various elements of the other types

These benign tumors, in general, fall into two main groups 1) small, frequently multiple tumors, varying in size from microscopic to one or two centimeters in diameter, found beneath the kidney capsule or in the superficial cortex They produce no clinical symptoms and are encountered most commonly as purely accidental findings at autopsy 2) Large solitary growths, discovered during life, cause symptoms and usually require surgery This paper will be devoted primarily to a consideration of this second group of large benign tumors

A review of the literature reveals a total in all age groups of 135 cases of benign tumor of the kidney large enough to be of clinical significance Among these cases there were 57 adenomas, 7 angiomas 17 fibromas, 24 lipomas, 22 myomas and 8 cases of mixed tumor Among the causes of childhood mortality in 1942 in the United States cancer and allied diseases stood third in the 3 to 10 years of age group (Dargeon) Next to the bones the kidney is the site most frequently affected by cancer in children In marked contrast to this is the extreme rarity of benign kidney tumors in children, there being only 14 cases ever reported (table 1) Because of the rarity of large benign renal tumors, especially in childhood, the author felt that it would be of interest to report the following case of a 43 pound fibroma occurring in an 8 year-old boy

## *Case Report*

A M , an 8-year-old African boy, entered Central Hospital (American Presbyterian Mission of French Cameroun) on October 11, 1954 with the chief complaint of 'a large abdomen " His parents stated that they had first noted a mass in the boy's abdomen at the age of 18 months and that, since that time, the mass had been slowly enlarging until the abdomen had reached its present enormous size In his earlier childhood the patient had led a normal existence and seemed to suffer no apparent adverse effects from the presence of the tumor However during the past three or four years, as the tumor began to assume its huge size, he had become progressively less active, tired easily, began to lose his appetite and complained of occasional abdominal discomfort and pain

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TABLE 1 *Large benign renal tumors occurring in childhood**

| Type of Tumor | Age | Sex | Size of Tumor | Description | Duration of Tumor | Author |
|---|---|---|---|---|---|---|
| 1 Adenoma | 11 mos | F | palpable tumor | adenoma | not stated | Czerny (1882) |
| 2 Adenoma | 2 yrs | — | palpable tumor | operated | not stated | Schonbron (188–) |
| 3 Adenoma | 16 mos | — | 6 5 × 5 × 5 cm | size of lemon | not stated | Kynock (1898) |
| 4 Adenoma | 3 yrs | F | palpable tumor | not given | not stated | Morris (1901) |
| 5 Adenoma | 12 mos | F | large | cystadenomatous kidney | not stated | de la Peña (1948) |
| 6 Adenoma | 4 mos | F | not stated | cystadenoma | not stated | Barrington-Ward (1950) |
| 7 Angioma | 4 days | M | palpable tumor in left flank | hemangioma autopsy finding | not stated | Szecsey & Flesch (1933) |
| 8 Angioma | 18 mos | F | 6 × size normal infant kidney | lymphangioma | not stated | Brown (1950) |
| 9 Fibroma | 11 yrs | — | not stated | from capsule lower pole kidney | 6 years | Wahl (1885) |
| 10 Fibroma | 2 yrs | — | 4 lbs | extensive cystic changes | since a few months after birth | Park (1886) |
| 11 Myoma | 1 yr | — | half tumor was 15 × 9 × 4 8 cm | bilateral rhabdomyomata | not stated | Constance (1947) |
| 12 Myoma | newborn | M | 7 × 5 × 5 cm | not given | present at birth | Zuckerman (1947) |
| 13 Mixed | 18 mos | M | 4 5 kg | polycystic adenomyxoma | 1 year or more | Söderlund & Wahlgren (1932) |
| 14 Mixed | 2 5 yrs | — | not stated | polycystic tumor | 1½ years or more | Bailey (1937) |

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* In 2 cases occurring in adults (Rush and Rush, Ochsner) the tumor was definitely known to be present from childhood, but since these are not strictly speaking "cases occurring in childhood" they are not included in this tabulation

During the past year he had been pretty much confined to bed and was able to get about only with assistance His state of general health had been going slowly downhill and he was becoming progressively weaker He did not complain of any urinary symptoms The patient was from a tribe in the neighboring country of Gaboon and, because of the language barrier, it was difficult or impossible to elicit any further history

Examination revealed a Negro of stated age who was weak, somewhat listless and slightly dyspneic at rest He preferred to lie on his right side The general

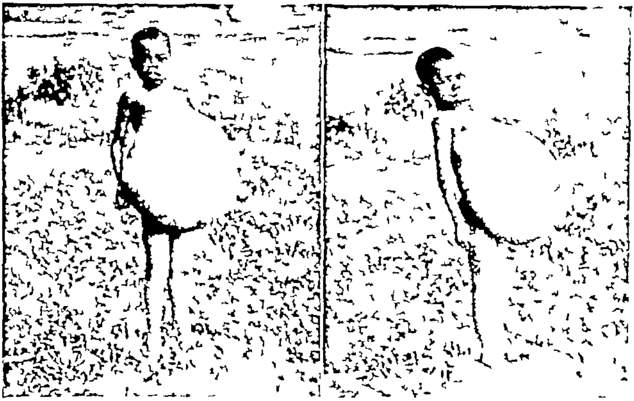

FIG 1 Eight year-old patient with abdomen enormously distended by 43 pound intrarenal fibroma Patient and tumor together weighed 94 pounds

examination was essentially within normal limits except for a mild tachycardia The point of main interest was the abdomen which was enormously distended (fig 1) The outline was smooth and no tenderness was present Neither a fluid wave nor shifting dullness could be elicited An enlarged liver was palpable in the right upper quadrant but the remainder of the abdomen was filled with a huge, rather firm, non tender smooth mass which could be easily palpated by rectal examination

Laboratory studies The hemoglobin was 10 0 gm, the white blood count 8,800 per cu mm Urine was negative for sugar, albumin and microscopically The stool and thick blood smear were negative for intestinal parasites and malaria

Hospital course The preoperative diagnosis was "large solid, probably benign, abdominal tumor, site of origin undetermined," although one of the examining doctors felt that it might be a case of ascites under pressure An attempted paracentesis however was unsuccessful in obtaining fluid Although the removal of such a large mass was a formidable undertaking and the risk of surgery was great in the patient's weakened condition, still it was apparent that he was going downhill rapidly and that an attempt at operative removal offered him his only chance of survival Consequently on November 2, 1954 he was taken to surgery

Operation Open drop ether anesthesia was used The abdomen was prepared and draped and a right midrectus incision was made from the xiphoid to the pubis which had to be enlarged later with a long transverse T extension of the main incision Shortly after the incision was made the patient began to have respiratory trouble and the heart became weak and irregular All supportive efforts were to no avail, the heart gradually getting weaker, blood pressure falling and finally the heart stopping altogether Prolonged efforts at cardiac massage also failed and the patient was pronounced dead about forty-five minutes after the operation started We were greatly puzzled as to what might have caused this peculiar chain of events leading to his death, which was quite different from anything we had ever experienced before In retrospect, the only plausible explanation is that, with the patient lying in the supine position on the operating table, the weight of the heavy tumor mass itself was sufficient to compress and occlude the inferior vena cava, thus depriving the heart of blood The loss of the patient in this way was doubly unfortunate because, as we found out later, it would have been fairly simple technically to remove the tumor

Autopsy A postmortem examination was made immediately after death The entire small bowel had been displaced to the right side and the transverse colon was tightly stretched over the anterior surface of the smooth, well-encapsulated tumor which completely filled the peritoneal cavity (fig 2) There were no adhesions or attachments to adjacent organs except for the transverse colon and mesocolon Several large, thin-walled blood vessels coursed over the surface of the tumor The only point of attachment of the entire tumor was to the left renal pedicle from which apparently the main blood supply was derived

Gross description The tumor arose from the lower pole of the left kidney, the upper pole perching like a little cap on top of the main tumor mass (fig 3, *A*) The upper kidney pole appeared grossly to be normal The tumor was smooth, well encapsulated, very firm (almost rubbery) in consistency and of a grayish-white color which in some areas had an orange hue The dimensions were 16 by 12 by 10 inches and it weighed 43 pounds (The patient, after the tumor had been removed, weighed only 51 pounds ) On cut section (fig 3, *B*) the tumor was seen to be solid and homogeneous and of an orangish-white color

Microscopic description The following description was given by Dr B G Lamson, assistant professor of pathology, School of Medicine, University of California Medical Center, Los Angeles

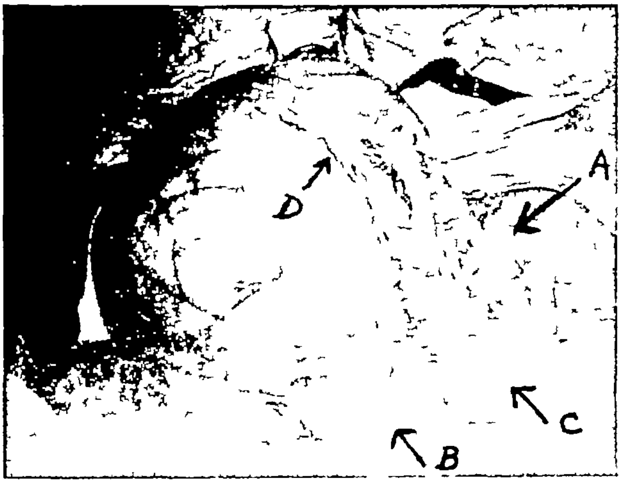

FIG 2 Fibroma delivered from abdomen at surgery *A*, upper extent (at xiphoid), *B*, lower extent (at pubis) of abdominal incision, *C*, small bowel, *D*, transverse colon tightly stretched over anterior surface of tumor

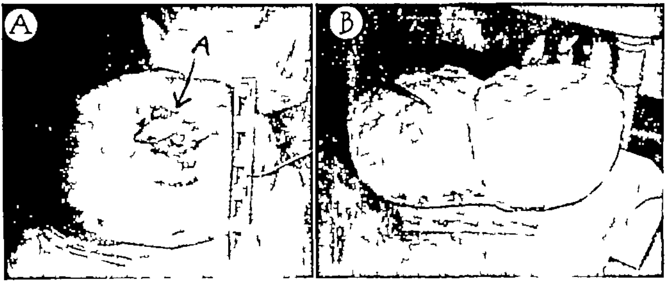

FIG 3 *A* tumor arose from lower pole of left kidney Upper kidney pole, *A* grossly appeared normal *B* on cut section tumor was solid homogeneous and orange white in color

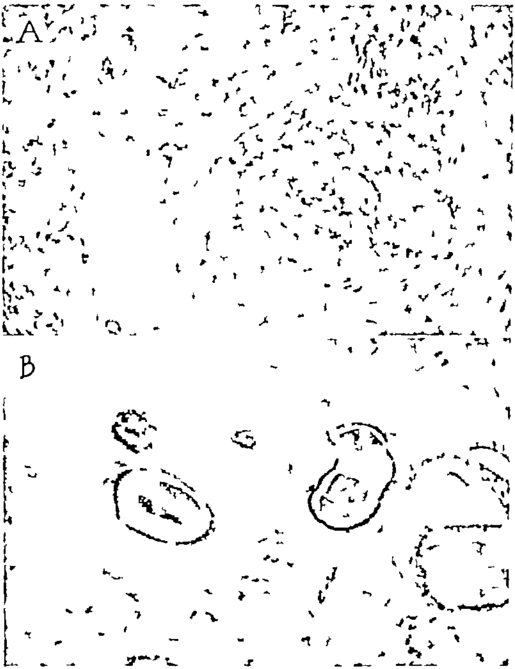

FIG 4 Low power photomicrographs *A* showing uniformly small and spindle shaped connective tissue nuclei of tumor *B* showing slightly dilated epithelial elements containing eosinophilic amorphous material

The tumor is primarily a growth of benign appearing connective tissue which is nonencapsulated at its junction with renal tissue, merging gradually into that organ In the junction zone many compressed and atrophic remnants of renal tubules are present along with an occasional cleft lined by epithelium of a double layer pseudo-stratified transitional type

The connective tissue component of the tumor which constitutes the great bulk of the growth is poorly cellular and varies in pattern Large areas show only wavy strands of delicate fibrils interspersed with small capillary blood vessels Other areas reveal larger bundles of connective tissue with prominent collagen deposition Occasional areas of cross layered fasciculation are seen In these regions larger blood vessels with thick hyalin walls without smooth muscle are prominent Mitotic figures or bizarre nuclear elements are not seen Connective tissue nuclei are uniformly small and spindle-shaped (fig 4, *A*)

Islands of adult type adipose tissue and focal aggregates of epithelial structures are very minor constituents of the tumor which do not appear related to the marginal zone of atrophied renal structures previously described Epithelial elements appear usually as small acinar and tubular structures lined by a columnar to cuboidal layer of single epithelial cells Many structures are slightly dilated and contain eosinophilic amorphous material (fig 4, *B*) More rarely flattened epithelial cells line extremely dilated multiloculated cyst-like structures presenting a cavernous hemangioma-like appearance Several circumscribed nodules of less orderly arranged epithelial cells show nests and strands of cells with uniform vesicular nuclei and indistinct cytoplasm within whorls of confining connective tissue

*Diagnosis Mixed mesodermal tumor (benign), chiefly fibroma but containing* small components of adipose tissue and epithelial structures

## DISCUSSION

*Age, sex, location and race* Large benign tumors of the kidney may occur at any age The youngest patient was a newborn (Zuckerman, Kershner, Laytner and Hirschl), 14 cases occurred in childhood (table 1) and the oldest patient was 81 years of age (Bailey and Harrison) The average age was 39 1 years Twice as many cases occurred in females as in males (76 females and 39 males out of 115 cases in which the age was stated) It is noteworthy that the lipomas are an exceptional group in that the ratio was 10 females to 1 male, while in all the other groups the ratio more nearly approached the 2 to 1 ratio There seemed to be no definite predilection for the side involved, whether right or left Although in many instances the race of the patient was not mentioned, there was a preponderance of white cases, only one case being recorded in the colored race (Gordon, Kimmelsteil and Caball) and one Chinese (Char and Pai)

*Size of tumor* For convenience of description we may divide renal tumors into three groups perinephric tumors, those arising from the renal capsule and intrarenal tumors Perinephric tumors sometimes assume colossal proportions, constituting some of the very largest growths known to pathologists and surgeons The largest of these are the lipomas The largest perinephric tumor on record

TABLE 2 *The largest recorded intrarenal benign tumors*

| Type of Tumor | Size | Author |
|---|---|---|
| Adenoma | 13 x 11 x 5 inches 22 lbs | Gordon Taylor |
| Angioma | 12 x 5 x 5 cm | Malashock & Kopp |
| Fibroma | 11 x 9 x 9 inches, 13 lbs | Rush and Rush |
| Lipoma | 25 x 19 x 12 cm 2250 gm | Bartsch |
| Myoma | 9 kg | Busse |
| Mixed | size of a child s head | Söderlund & Wahlgren |

is that of Hirsch and Wells which was explored, found to be an inoperable liposarcoma, and at autopsy weighed 69 pounds McConnell's tumor was the largest benign perinephric tumor ever reported It was a fibrolipoma weighing 65 pounds, removed at surgery, but recurring 7 years later with malignant changes Although quite rare in childhood benign perinephric tumors have been reported Lauwers cited the case of a 7 year-old child from whom a 6 pound lipoma was removed and Bork reported the case of a perirenal lipoma operated in a 1 year-old girl

The two largest benign tumors arising from the renal capsule are those cited by Demel, one of which was a fibrolipoma weighing 29 kg (63 8 pounds) and the other a lipoma weighing 63 pounds Reverdin reported a fibromyoma of the renal capsule weighing 48 pounds, Bruntzel had a 37¼ pound capsular fibroma and Tillman reported a capsular fibromyxoma weighing 10 kg (22 pounds)

The largest of the intrarenal tumors are listed in table 2 There is some question, however, about the largest fibroma Hektoen and Riesman state that "in rare cases fibromas attain a very large size, thus Wilks observed one which weighed 37½ pounds " However in Wilks' original paper he merely says, 'the right kidney was converted into a tumor the size of a young child's head" and he says nothing about the weight It is not clear therefore where Hektoen and Riesman got the figure of 37½ pounds, unless perhaps they were referring to Bruntzel's case of a capsular fibroma which weighed 37¼ pounds Consequently, because of this confusion, we have given Rush and Rush credit for the largest intrarenal fibroma to date

From a consideration of these data it appears that the tumor being reported in this paper, which weighed 43 pounds, is not only the largest fibroma of the kidney but it is also the largest benign tumor of any kind, arising from the kidney itself, ever to be reported

*Origin and classification* Fuchsman and Angrist classified benign renal tumors into epithelial and connective tissue types The various kinds of adenomas make up the epithelial type and the connective tissue tumors are the fibroma, myoma, lipoma and a small mixed group The mixed group are tumors made up of various combinations of smooth muscle, fibrous tissue, adipose tissue and occasionally tubulo-epithelial elements, such as the fibromyolipoma, adenofibromyxoma, etc The multiplicity of theories purporting to explain the origin and nature of the benign renal tumors is an index of the complexity of the problem There are two main schools of thought The first favors the idea that these tumors are developmental or congenital in origin and the second that they are neoplastic in origin

Colvin, an advocate of the developmental theory, listed the pathogenesis as follows 1) from the wolffian body, 2) from renal blastema or nephrotome, 3) from a faulty segmentation of the nephrotome from the myotome and sclerotome, 4) from primordial segments or undifferentiated mesoderm included in the nephrogenic anlage, and 5) from endothelium Fuchsman states, "The basic linkage of these tumors is best seen in the mixed group The adenomyomas, fibromyolipomas and the other permutations and combinations of epithelial and stromal tissues may properly be considered differentiated forms of Wilms's tumors The diversified character of these neoplasms suggest that they are developmental tumors which, though differentiated, have a common embryonal origin Some epithelial neoplasms and connective tissue tumors, and particularly the mixed forms, probably have a common origin, representing varying differentiation of original nephrogenic mesenchyme "

On the other hand advocates of the neoplastic theory, such as Bailey and Herbut, believe that benign renal neoplasms may arise from any of the various elements of the kidney, originating from the tissues which they appear to represent or be derived from, as for example, lipoma from fat cells or their progenitors, fibroma from connective tissue cells or their progenitors, etc

There is an additional theory regarding the origin of the adenomas and lipomas, i e , that, in the case of the adenomas, they are a result of a reparative process and arise in association with arteriosclerotic and degenerative changes in the kidney, while in the case of lipomas they are the result of a degenerative process within the kidney resulting in fatty replacement

Since benign renal tumors, especially the larger ones, are seldom "pure" but rather are composed of two or more types of tissue in various combinations, one author (Watson) advocated calling all benign renal tumors "mixed tumors," suggesting that this group of tumors constitute a definite variety which probably arise in a manner not unlike mixed tumors in other locations The present writer believes, however, that, although there is a great similarity among these tumors in gross appearances, clinical manifestations, symptoms, operative problems and prognosis, and from a practical standpoint they can be described together as a single group, yet (as Simon pointed out) these tumors fundamentally do not appear to have characteristics in common such as are possessed by the malignant types of mixed renal tumors but rather resemble the tumors of their predominant tissue Their constituent tissues are practically always closely related and arise from one germinal layer only Considerable confusion would be avoided if we continue to classify them according to the predominant tissue or tissues rather than to group them collectively as mixed tumors

*Symptomatology* The symptoms of the various types of benign renal tumors, with the exception of angioma, are similar When they are small, there are no clinical manifestations referable to the kidney When they are large, however, they may give rise to various symptoms, the most constant being the presence of a tumor The patient has often been aware of its presence for a long period, in one instance for 14 years In more than half the cases gross hematuria is present, although it is infrequent in fibroma and myoma It is usually rather mild but *often of long duration Occasionally it may be quite severe and sudden in onset* Pain was present in the majority of cases, usually of a dull, aching character in the renal area over the involved kidney but occasionally producing severe attacks of colic from the passage of blood clots Urinary symptoms may be noted occasionally, but are not at all common Fever, when it occurs (infrequently), is usually the result of infection of the urinary tract from obstruction or *gross degeneration of the tumor Renal function is usually* reduced on the side involved In addition, very large tumors (such as the one being reported) may produce pressure upon the diaphragm, displacement of the intestines and spleen, and, occasionally, pressure upon the pelvic organs

In the case of hemangioma, there is usually no palpable tumor and intermittent mild or profuse hematuria is the only symptom The bleeding is often very severe and may produce marked anemia or shock The impairment of renal function is usually less than with other types of tumor There is a peculiar lack of clinical data, especially in the smaller tumors, on which to base a diagnosis of hemangioma In several instances the diagnosis of essential hematuria had been made, but the bleeding continued, obviously from only one kidney, and, after other causes had been carefully ruled out, nephrectomy was performed and the hemangioma found It frequently happens that the diagnosis cannot be made even with the kidney in view because these tumors are located usually in the interior of the kidney

*X ray diagnosis* Bailey found that much useful diagnostic information could be obtained from three types of roentgenological studies, i e , the plain film of the abdomen, the pyelogram and the barium enema The plain film shows the outline of the large mass In some cases calcification may be demonstrated within the tumor, but this feature in itself is not of great assistance because an occasional malignant renal neoplasm (hypernephroma) will also contain areas of calcification The plain film is of especial value in demonstrating the absence of metastatic lesions in bone which are frequently found in malignant renal tumors of this size

Pyelogram When the tumor is primarily intrapelvic or encroaches upon the kidney pelvis secondarily, pyelographic data may be typical of renal tumor If encroachment upon or compression of the renal pelvis does not occur, the pyelogram will be normal which, according to Kretschmer, occurs most often when the tumor originates in the lower pole of the kidney No deductions can be drawn from the pyelogram itself which are sufficiently definite to warrant a positive preoperative diagnosis of benign renal neoplasm There are, however, certain features which may suggest this diagnosis Usually one sees displacement *of the renal pelvis either at the top or at the bottom of the mass Its outline is* distorted in a smooth, regular manner, usually with marked elongation of one or more calyces A malignant tumor of this size would almost certainly have invaded the renal pelvis so as to produce a grossly irregular filling defect Small malignant renal tumors sometimes give a smooth filling defect but this has not been encountered in malignant tumors of the size of these under consideration In angioma the pyelogram is often normal, although in the presence of gross bleeding clots may partially fill the pelvis and produce false filling defects In some instances a mottled appearance has been noted which was thought to be characteristic of angioma

The barium enema shows the extent and direction of displacement of the colon, thus confirming the size of the mass and demonstrating that it is not connected with the bowel Roentgenographic studies of other areas, especially of the chest, are of value in excluding metastases

*Differential diagnosis* The differential diagnosis of large benign renal tumors include malignant renal tumors, splenomegaly, retroperitoneal neoplasms, cysts of the mesentery, pancreas and ovary, hydronephrosis, ascites and pregnancy A large mass in the flank may result from growths, neoplastic or otherwise, of several viscera When a patient is seen who has a very large neoplasm in the renal fossa, the usual supposition is that such a mass is malignant The discovery of a large retroperitoneal mass in infancy and childhood leads one immediately to a consideration of the two most common lesions in that age group, i e , neuroblastoma and Wilms' embryoma of the kidney Occasionally, however, as we have already seen, the surgeon is surprised to find instead a large benign tumor One may suspect that a large renal or retroperitoneal mass is not malignant when the tumor or symptoms have been present over a long period of time with little effect on the general health of the patient and, particularly, when no demonstrable evidence of metastases can be found Helpful points of differentiation in the pyelogram between benign and malignant lesions have already been given

The spleen is an organ very frequently enlarged and in several cases the exclusion of the diagnosis of splenomegaly was difficult In favor of renal neoplasm are the normal leukocytic count, the distortion of the renal pelvis, the displacement of the kidney itself and the palpation of a mass, separable from the tumor, in the left hypochondrium An enlarged spleen usually has a well-defined notch It is often difficult to exclude a retroperitoneal neoplasm The only definite point of differentiation lies in the deformity of the renal pelvis produced by a benign renal tumor, usually showing a marked elongation of a single calyx in the pyelogram Cysts of the mesentery, pancreas and ovary do not displace the kidney or cause distortion of the renal pelvis Hydronephrotic kidneys may occasionally attain tremendous size In these cases satisfactory cystoscopic investigation with pyelography will make the differentiation clear Ascites and pregnancy should be mentioned

*Operation* It is important for the surgeon to keep in mind that not all renal tumors of surgical import are necessarily malignant Most authors, therefore, believe that patients in whom no evidence of metastases can be demonstrated should always be subjected to operative exploration, especially in view of the favorable prognosis of such lesions The problem of operative removal of large benign renal tumors is concerned chiefly with the correct approach This must be one in which adequate room can be secured to permit removal of the mass and at the same time one which makes the renal pedicle accessible These criteria are best met by a transperitoneal approach Occasionally a combined thoraco-abdominal incision may be necessary to get the proper exposure (Mortensen)

Practically all authors are agreed that nephrectomy combined with complete removal of the intact tumor is the procedure of choice On rare occasions a local resection of the tumor has been accomplished successfully, but this is not recommended by most authors because, at the time of surgery one cannot be completely sure of its benignity

*Pathologic appearance* Adenoma Grossly the adenomas vary in size from microscopic to 13 inches in diameter and weigh up to 22 pounds They are sharply circumscribed but not encapsulated Generally they are solid, gray, grayish white, yellowish or brown and moderately firm Occasionally they may be cystic and contain papillary projections into the lumen Large ones compress and destroy adjacent kidney substance The kidneys in which the adenomas arise may be normal, or more frequently, they are small, contracted and sclerotic

Histologically, benign adenomas fall into three categories with transitional stages between them 1) tubular, 2) papillary, and 3) alveolar The tubular adenoma tends to reproduce small renal tubules closely packed together The papillary type consists of fluid filled cysts with papillary projections Alveolar adenoma is characteristically arranged in columns or cords of cells which resemble on the one hand adrenal tissue and on the other hand low grade clear cell renal carcinoma The difference histologically between a benign adenoma and an adenocarcinoma is usually clearcut, but on occasion the line of demarcation may be extremely difficult or impossible to establish Many authors hold that the adenoma may be transformed into a carcinoma and some even go so far as to consider all "adenomas" as malignant growths

Angioma The hemangioma varies in size from pinpoint to 12 cm in diameter As it enlarges it compresses the adjacent renal substance to form more or less a pseudocapsule, but a true capsule is not present The tumor is hemorrhagic or deep red in color, moderately firm and more or less solid Sometimes it is composed of sponge like spaces filled with blood At other times there may be degeneration and necrosis of tissue with formation of large cystic spaces filled with blood Microscopically it usually consists of cavernous sinuses lined with flat endothelium, similar to those found in the liver and other organs Hemangiomas are apt to be pure in type but angiomatous tissue may rarely be present in combination with other types of benign renal tumor tissue in the "mixed group"

In the only recorded case of lymphangioma (T T Higgins) no description is given of the lesion but a photograph shows a multiloculated, cystic, apparently encapsulated, tumor about six times the size of the normal kidney

Fibroma The fibromas vary in size from a few millimeters to 11 inches in diameter and weigh up to 13 pounds They are usually sharply circumscribed, solid and moderately firm and of a homogeneous, grayish white appearance They are frequently mentioned as having undergone mucoid and pseudocystic degeneration in portions The histologic appearance varies considerably from case to case It may be composed of dense, sclerotic hyalinized fibrous tissue, or the entire tumor may be made up of more or less loose edematous, even myxomatous connective tissue cells In still other cases the entire tissue may be quite cellular so that differentiation from fibrosarcoma may be extremely difficult or even impossible

Lipoma Lipoma of the kidney is a true tumor and should not be confused with another lesion known as lipomatosis or fatty degeneration The lipomas in the kidney area are divided into three varieties depending upon their location, i e, retroperitoneal, perirenal and renal (or intrarenal) We are concerned only with the intrarenal lipomas in this paper They vary in size from a few millimeters to 25 cm in diameter They are generally sharply circumscribed, covered with a thin capsule, smooth and glistening on the outside, and flabby, pseudofluctuant or hard and fibrotic upon palpation Cut surfaces show a multiloculated, reddish- or yellowish-gray, typically fatty tissue interspersed with which are fibrous trabeculae and varying numbers of blood vessels Histologically the tumor consists of typical adult fat cells The stroma is generally scanty and is composed of well-vascularized loose connective tissue, which on occasion, however, may be more dense and collagenous It frequently exhibits some degree of mucoid degeneration Myxomatous tissue and smooth muscle may occasionally be present

Myoma The myoma varies in size from a few millimeters to 38 cm in diameter, weighing as much as 9 kilograms Like the fibroma, the exposed external surface is well-encapsulated, smooth and glistening The tumor is generally firm to hard, solid, and on section discloses a characteristic pearly-gray appearance Occasionally it may undergo cystic degeneration or calcification Microscopically it is composed of typical smooth muscle cells which are elongated or spindle-shaped The leiomyoma may be difficult to distinguish histologically from a fibroma, requiring the employment of special stains Often there is also connective tissue, adipose tissue or myxomatous tissue present

Rhabdomyoma has been reported in only one case (Constance) It was lobulated and well-encapsulated, presenting a solid, opaque brownish whorled appearance on cross-section Histologically only one type of tissue was present—interlacing bundles of well formed muscle fibers, many of which contained longitudinal and cross striations

*Prognosis* Generally speaking, the prognosis for the whole group of large benign renal tumors has been very good Adequate follow up studies are lacking in the majority of cases so that a statement as to the final outcome cannot be made However, most authors feel that in the absence of malignant changes the ultimate outlook for the patient is favorable

*Complications* It is interesting that about half the cases of tuberous sclerosis of the brain are associated with bilateral benign tumors of the kidney Cases have been recorded in which a benign tumor changed into a malignant tumor and many authors contend that adenomas undergo a slow transformation into clinical carcinoma Some benign tumors may increase in size to such an extent that they produce pressure and obstruction of the ureter and pelvis, the portal system, spermatic vein, and diaphragm, resulting respectively in hydronephrosis and pyelonephritis, ascites, varicocele and dyspnea Severe hemorrhage may occur occasionally, especially in angioma In some instances, bleeding may occur directly into the tumor or the surrounding tissue Such an accident produces severe pain, rapid enlargement of the tumor and sometimes rigidity of the overlying abdominal muscles and general symptoms of hemorrhage

## SUMMARY

Large benign tumors of the kidney are discussed and the literature reviewed to date

A case is reported of a 43-pound fibroma occurring in childhood

As far as could be determined from the literature, this case is 1) the 136th case of large benign renal tumor to be reported, 2) the 18th case of renal fibroma, 3) the third case of renal fibroma in childhood 4) the second case of large benign renal tumor to occur in a Negro and 5) the largest benign tumor of any type, arising from the kidney, ever to be reported

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# THE PELVIC URETER IN THE MALE AND FEMALE

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In most of the anatomical texts and special descriptions of the topography of the pelvic ureter it is stated that the ureter, after crossing the brim of the pelvis, descends to the level of the ischial spine and then turns forward and medially, running on the floor of the pelvis until it enters the wall of the bladder J E Markee,[1] for instance, in his account on the ureter in Morris' HUMAN ANATOMY (11th ed , 1953, p 1509) presenty the topography of the pelvic ureter in the following manner "The pelvic portion begins above at the pelvic brim and courses downward, inclining slightly laterally and posteriorly to conform to the curvature of the lateral pelvic wall Reaching the pelvic floor, it bends anteriorly and medially at about the level of the ischial spine to reach the bladder " In our dissections of the ureter in embalmed cadavers, however, we never saw the ureter descending to the ischial spine before it makes its forward turn nor did we ever see it on the pelvic floor We described the course of the ureter in the following terms (Uhlenhuth, Hunter and Loechel, 1953[2]) After crossing the brim of the pelvis the ureter descends for a distance within the hypogastric root, in front of the greater sciatic notch and in close vicinity to the ventral division of the hypogastric artery Considerably above and ventral to the ischial spine the ureter leaves the hypogastric root and, making an angle (ureteral angle) of variable size, enters the vesicohypogastric fascia (ventral wing of hypogastric fascia), in this it passes forward and medially to the end of its course, keeping always a considerable distance above the pelvic floor As these observations were made with accurate methods only in six pelves of the research laboratory (dissections and radiograms) and in eight pelvic dissections of the student dissecting laboratory, it was decided to check them again in a more systematic manner and in a larger number of specimens, both male and female

Moreover, from the location of the ureteral orifice in the radiograms it appeared that the female pelvic ureter is longer than the male pelvic ureter, although, as stated by Schwalbe,[3] the total length of the ureter is greater in the male than in the female As no reference to this difference between the ureter in the two sexes is made in the recent literature, the pelvic ureters were measured and an attempt was made to find the cause of this difference

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## MATERIAL AND METHOD

For the purpose of obtaining the measurements necessary for this investigation, two lateral radiographs, one from the right side for the right ureter, and one from the left side for the left ureter, were made of each pelvis In preparing the pelvis, after it had been separated from the trunk at the level of the third or fourth lumbar vertebra and after the lower extremities had been removed by a saw cut at the middle of the thigh, all soft parts, including the external genitalia, were removed from the outside of the pelvis and the remaining portions of the femurs were disarticulated in the hip joint and removed The ureters were injected with a thick barium paste, the bladder was incised by a median sagittal incision, the vesical orifices of the ureters were marked by inserting a small lead pellet, and all the important landmarks were painted with radiopaque paint

In order to obtain comparable reference lines all exposures were made with the pelvis held firmly in a vise type aligner in such a position that superior anterior iliac spines and pelvic tubercles were located in the same vertical plane

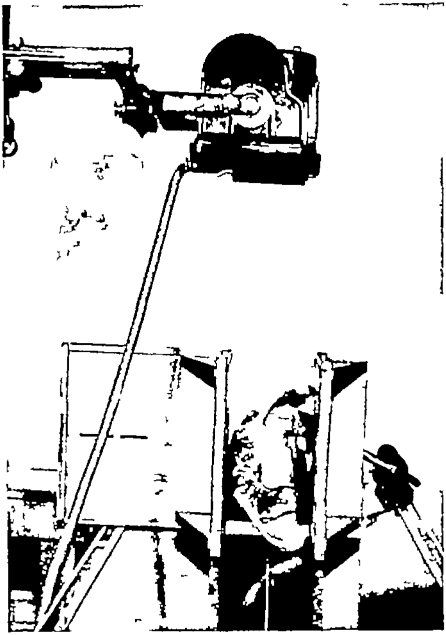

Fig 1 Specimen in aligner stand on x ray table in position for taking right aspect radiograph

(fig 1) Since our x-ray apparatus permitted exposures only from above, the pelvis and aligner had to be laid on the right side for exposure of the right ureter and turned on its left side for exposures of the left ureter In these positions the superior anterior iliac spine of the side to be x-rayed was close to the film (fig 1, exposure for the right ureter)

All exposures were made with the x-ray tube 30 inches distant from the table top, the pelvis centrally placed with respect to the central ray, and the film holder placed in the Potter-Bucky diaphragm beneath the table

Ten male (No 11 to 20) and ten female (No 1 to 10) pelves were used, yielding for comparison 20 male and 20 female ureters After the exposures for the radiograms had been made the ureters were removed and measured directly As the conventional landmark for the cranial end of the pelvic ureter cannot be used for accurate measurement of the length of the pelvic ureter, the point on the ureter opposite the caudal margin of the fifth lumbar vertebra was chosen as the point of commencement of the pelvic ureter

All other measurements required in this study were taken from the radiographs, they are shown in the standard diagram of figure 2, and their individual values are listed in tables 1 and 2 for the 10 males and 10 females respectively As indicated in figure 2, all measurements were referred to two standard lines, a "vertical line" (AA) and a "horizontal line" (BB′) intersecting the line AA at an angle of 90° and containing the ischial spine

A collateral study was made of the distance between the vesical orifice of

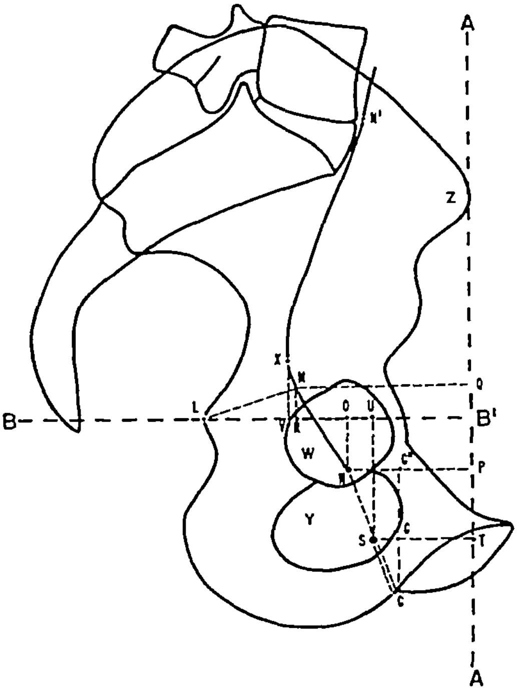

FIG 2 Tracing of radiograph of right lateral view of ureter and bony pelvis of female showing principal measurements taken

TABLE 1 *Measurements taken from 10 male pelves in mm*

(Consult fig 2)

| Symbol | Specimen | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | Av |
| Bony pelvis | | | | | | | | | | | |
| L-B′ | 129 | 120 | 141 | 141 | 128 | 127 | 124 | 133 | 124 | 128 | 130 |
| Ureteral Angle | | | | | | | | | | | |
| N V | 47 | 21 | 32 | 44 | 40 | 50 | 51 | 24 | 63 | 30 | 40 |
| L V | 49 | 67 | 32 | 45 | 38 | 49 | 42 | 57 | 34 | 31 | 44 |
| Ureter | | | | | | | | | | | |
| *N′ N | 105 | 112 | 105 | 140 | 137 | 150 | 123 | 120 | 144 | 143 | 129 |
| L M | 43 | 62 | 36 | 56 | 44 | 55 | 28 | 50 | 23 | 37 | 44 |
| M R | 10 | 3 | 11 | 29 | 20 | 14 | 13 | 12 | 0 | 15 | 13 |
| L-R | 41 | 63 | 36 | 48 | 39 | 54 | 25 | 58 | 22 | 34 | 42 |
| M Q | 88 | 57 | 106 | 94 | 89 | 73 | 99 | 76 | 102 | 94 | 88 |
| O N | +8 | −21 | +9 | −11 | +9 | −6 | +13 | −13 | −11 | −14 | −4 |
| N P | 85 | 51 | 105 | 65 | 91 | 67 | 98 | 74 | 98 | 76 | 80 |
| N G | 95 | 52 | 98 | 64 | 77 | 63 | 100 | 62 | 80 | 60 | 75 |
| G-G″ | 83 | 51 | 68 | 54 | 62 | 52 | 78 | 56 | 41 | 44 | 59 |
| G N | 47 | 5 | 71 | 33 | 44 | 34 | 63 | 26 | 67 | 40 | 43 |
| Bladder Condition† | D | C | D | D | D | D | D | C | D | C | |

These figures represent the average of measurements taken from the films of the right and the left aspects of the specimen An asterisk preceding the symbol indicates actual measurements made from the specimen

† D = distended C = contracted

the urethra and the inferior end of the symphysis pubis For this purpose four pelves, two male (Nos 19 and 23) and two female (Nos 21 and 22) were used Before the exposures described above were taken, a lead pellet was inserted into the urethral orifice, after the exposures had been made, the pelves were divided by a midsagittal section, the ureters were removed and measured as described for the pelves Nos 1–20, and, in addition, the distance between urethral orifice and inferior end of symphysis pubis was measured in the cadaver (table 7)

## CRITICAL ANALYSIS OF OUR X RAY METHOD

In figure 3 photographs of two of our right-side radiographs, one of a female and one of a male, are shown Inspection of these as well as of the standard diagram (fig 2) shows that although superior anterior iliac spine and symphysis pubis were located in the same vertical plane of the aligner, the symphysis pubis (ventrocranial end) projected beyond the vertical reference line AA This discrepancy is due to the fact that in taking the x ray exposures the superior-anterior iliac spine was closest to the plane of the film, the symphysis pubis farthest away from it and, therefore, magnified in the film In fact all the structures between the sagittal plane of the iliac spine and that of the symphysis

TABLE 2 *Measurements taken from 10 female pelves, in mm*
(Consult fig 2 )

| Symbol | Specimen | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Av |
| Bony Pelvis | | | | | | | | | | | |
| L-B′ | 115 | 109 | 126 | 119 | 116 | 125 | 121 | 121 | 107 | 117 | 118 |
| Ureteral Angle | | | | | | | | | | | |
| X-V | 23 | 32 | 38 | 50 | 40 | 39 | 44 | 33 | 27 | 34 | 36 |
| L-V | 16 | 30 | 32 | 20 | 33 | 27 | 65 | 43 | 46 | 39 | 35 |
| Ureter | | | | | | | | | | | |
| *X′-X | 184 | 132 | 141 | 160 | 121 | 159 | 126 | 130 | 131 | 130 | 141 |
| L-M | 16 | 32 | 33 | 27 | 43 | 27 | 71 | 45 | 51 | 44 | 39 |
| M-R | 3 | 11 | 14 | 11 | 23 | 6 | 18 | 14 | 15 | 17 | 13 |
| L-R | 16 | 30 | 31 | 25 | 35 | 28 | 68 | 43 | 48 | 40 | 36 |
| M Q | 100 | 79 | 95 | 95 | 82 | 97 | 53 | 78 | 59 | 77 | 82 |
| O-X | −50 | −19 | −23 | −39 | −7 | −42 | −19 | −19 | −21 | −20 | −26 |
| X-P | 74 | 59 | 78 | 65 | 66 | 91 | 37 | 63 | 42 | 58 | 63 |
| X-G | 52 | 45 | 53 | 41 | 61 | 61 | 56 | 47 | 48 | 49 | 51 |
| G G″ | 5 | 38 | 36 | 17 | 47 | 24 | 54 | 39 | 47 | 44 | 35 |
| G″-X | 50 | 23 | 38 | 36 | 37 | 55 | 8 | 25 | 10 | 20 | 30 |
| Bladder Condition† | D | C | D | D | C | C | C | C | C | C | |

These figures represent the average of measurements taken from the films of the right and the left aspects of the specimen An asterisk preceding the symbol indicates actual measurements made from the specimen

† D = distended, C = contracted

pubis are magnified in the radiogram, the magnification being the greater, the closer the structure is to the plane of the symphysis pubis

For this reason only the values obtained by direct measurement (length of ureter, distance between vesical orifice of urethra and inferior end of symphysis pubis) represent the true values, all the measurements obtained from the radiograms are only an approximation to the true values, but since all the pelves were x-rayed with the same technique, our x-ray values are comparable (between each other)

### *Ureter and Ischial Spine*

When the ureter is studied in the conventional ventrodorsal radiogram (fig 4), the appearance is created that the ureter descends actually to the ischial spine before it makes the angle If, however, a radiogram is taken in craniocaudal direction (fig 5) it becomes immediately evident that the impression gained from a ventrodorsal exposure is a deception, the ureteral angle lying actually far away in ventral direction from the ischial spine Craniocaudal radiograms give, however, no information as to whether the ureteral angle lies in the same transverse plane as the ischial spine, or in a position cranial or caudal to this plane, such information can be obtained only from lateral exposures, such as were used in this study (fig 3) Although these yield accurate information of

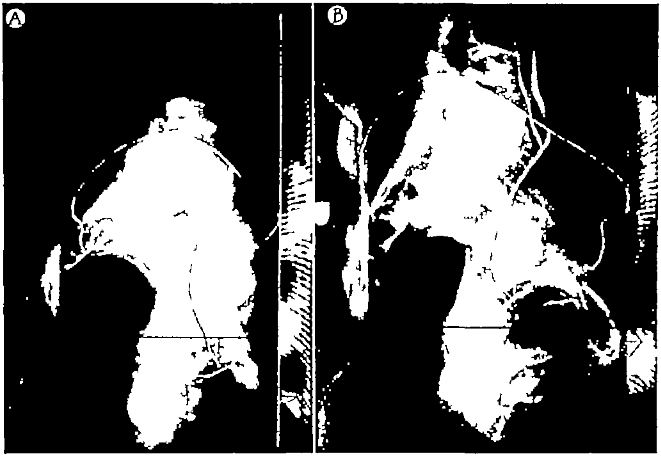

Fig 3 A photograph of radiograph of female pelvis No 9, taken from right side Illustrating vertical reference line horizontal reference line right ureter and its orifice angle of right ureter right ischial spine caudal and cranial ends of symphysis pubis, promontory and caudal border of fifth lumbar vertebra

*B* photograph of radiograph of male pelvis No 14 taken from right side Illustrating vertical reference line, horizontal reference line right ureter and its orifice angle of right ureter right ischial spine caudal and cranial ends of symphysis pubis promontory and caudal border of fifth lumbar vertebra

both the craniocaudal and the dorsoventral relationship between ureteral angle and ischial spine, the appearance of the angle of the ureter is not so sharp as it is in dissections (fig 6) and in craniocaudal x ray exposures (fig 5) In the body the ureteral angle is produced by a change in two directions, ventral and medial, but the medial component does not find expression in a lateral exposure since it lies in the plane of the rays Nevertheless, as is shown in the radiograms (fig 3) and in the tracings of the 20 right ureters made from the films (figs 7 and 8), it is possible to determine the location of the ureteral angle with an accuracy sufficient for our purpose

As is shown in the standard diagram (fig 2) the relation of the ureteral angle to the ischial spine was ascertained in the radiograms by two measurements VX being the cranial distance, VL the ventral distance of the ureteral angle from the ischial spine The average values of these two measurements are shown in table 3 (for individual values see tables 1 and 2)

In all 20 pairs of ureters the ureteral angle was located invariably cranial and ventral to the spine of the ischium Moreover, the distance between these two landmarks was considerable in both directions the values being about one and one half inches This means that the ureter is not even near the ischial spine when it makes its forward turn, leaves the hypogastric root and enters the ventral hypogastric fascial wing

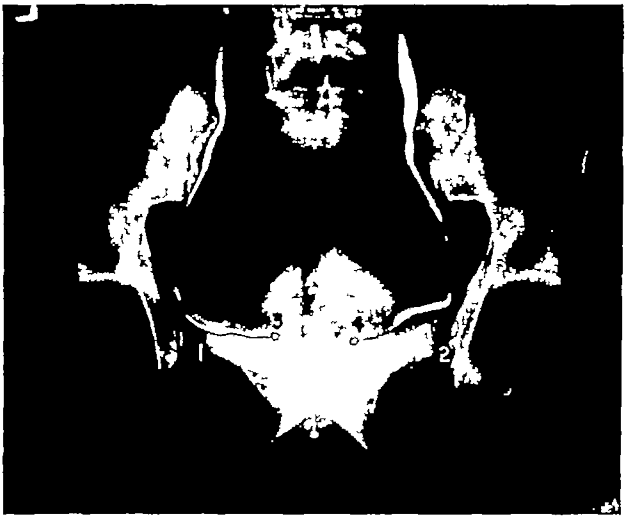

Fig 4 Photograph of radiograph of male pelvis, ventrodorsal view *1*, Encircled wire indicating left ischial spine *2*, Encircled wire indicating right ischial spine *3*, Ureteral orifice of left ureter *4*, Ureteral orifice of right ureter Lateral borders of ureters outlined with India ink

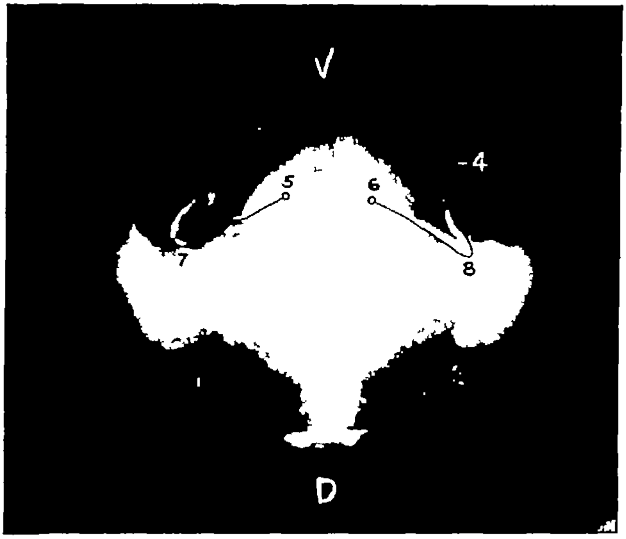

Fig 5 Photograph of radiograph of male pelvis, craniocaudal view *V*, ventral *D*, dorsal *1*, Encircled wire indicating left ischial spine *2*, Encircled wire indicating right ischial spine *3*, Commencement of pelvic portion of left ureter *4*, Commencement of pelvic portion of right ureter *5*, Ureteral orifice of left ureter *6*, Ureteral orifice of right ureter *7*, Angle of left ureter *8*, Angle of right ureter

Not only does the angle of the ureter lie a considerable distance from the ischial spine, but the ureter does not come close to the spine in any part of its course This is shown in table 4 in which the closest distance between ureter and ischial spine is recorded for 20 male and 20 female ureters (see tables 1 and 2 for individual values)

In the males the ureter never came closer to the ischial spine than 23 mm (see table 1), in the females the shortest distance was 16 mm But in some cases

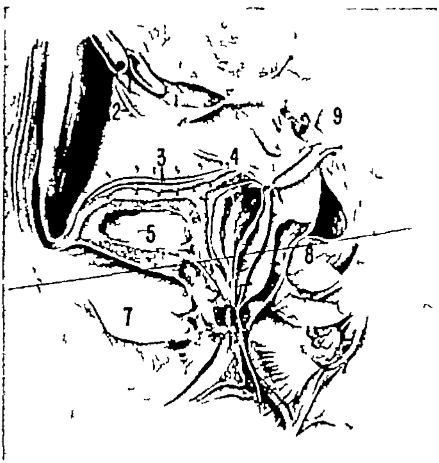

Fig 6 Right half of male pelvis illustrating relation between ureteral angle and ischial spine *1* Hypogastric artery *2*, Ureter in hypogastric root *3* Ductus deferens *4* Dot on ureter ureteral angle *5*, Interior of bladder *6* Seminal vesicle *7*, Symphysis pubis *8*, Dot in rectum representing position of ischial spine *9* Sacrum (Uhlenhuth Hunter and Loechel Problems in Anatomy of Pelvis fig 2 Philadelphia J B Lippincott Co )

the closest distance between ureter and ischial spine was more than 2 inches (62 mm in the males, 71 mm in the females)

Usually the point at which the ureter comes closest to the ischial spine lies at a level cranial to the level of the spine (horizontal reference line BB′), only in one single instance was this point in the same transverse plane as the spine (male No 19) Moreover, in every single case the closest point of the ureter was caudal to the ureteral angle

From these observations it is evident that the ischial spine cannot be used as a landmark in the description of the course of the ureter

### LENGTH OF PELVIC URETER

As table 5 shows, the female ureters are 12 mm (about one-half inch) longer than the male ureters There is, however, a considerable degree of overlapping, since six male ureters are longer than the shortest female ureter Still it is found that, on the average, the five longest female ureters are 10 mm longer than the 5 longest male ureters (155 and 145 mm average, female and male respectively), and again that the 5 shortest female ureters are 15 mm longer than the 5 shortest male ureters Moreover, the longest female ureter exceeds in length the longest male ureter by 25 mm , and the shortest female ureter is 16 mm longer than the shortest male ureter

It is evident that there must be some cause for this difference in length First, we thought the functional condition of the bladder, whether contracted or

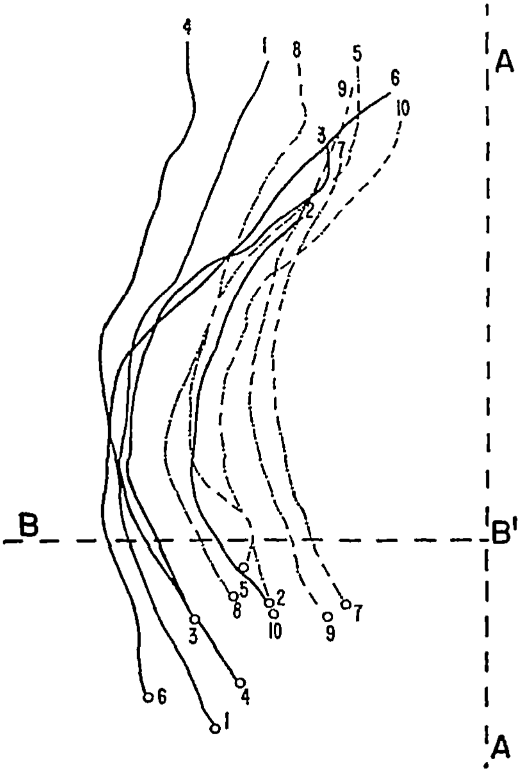

FIG 7 Tracings, from film, of ten right female ureters Solid lines five longest pelvic ureters Dot dash line five shortest pelvic ureters AA vertical reference line BB′ horizontal reference line

relaxed, might influence the length of the ureter It soon became evident that the greater length of the female ureter was unrelated to the state of the bladder Then we checked the length of the ureter against the size of the pelvic cavity, but found that the female ureter is longer not only absolutely, but also relatively to the size of the pelvic cavity

In searching for other causative factors, we re-examined the values of the ventral distance of the angle of the ureter from the ischial spine As is seen in table 3, in the female the ureteral angle seems to lie nearly 10 mm closer to the ischial spine This relation suggested to us at first, that in its descent into the pelvic cavity the ureter passes down in a more dorsal direction in the female so that the distance it has to run through from the angle to the bladder would be longer than in the male The value of 10 mm closer to the spine was especially suggestive as the female ureter is approximately that much longer (12 mm ) than the male ureter However, in checking the distance of the ischial spine from the vertical reference line AA, it was found that in the female the spine lies 12 mm more ventrally than in the male, the average distance (LB′) between ischial spine and reference line AA being 130 mm in the male and only 118 mm in the female (for individual values see tables 1 and 2) In addition, it was found that the distance between the ureteral angle (X on fig 2) and the reference line

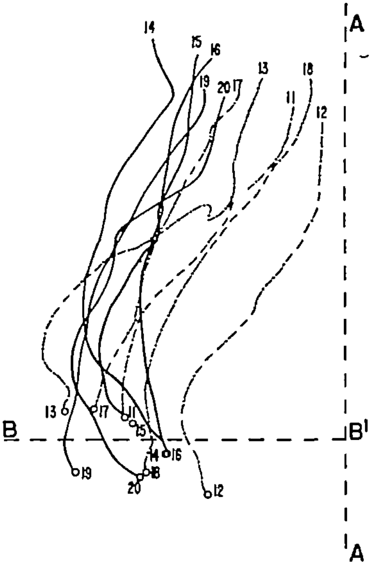

Fig 8 Tracings from film of ten right male ureters Solid line five longest pelvic ureters Dot-dash line five shortest pelvic ureters AA vertical reference line BB' horizontal reference line

Table 3 *Average distance of ureteral angle from ischial spine (in mm)*

| | Cranial Distance of Angle from Spine VX | Ventral Distance of Angle from Spine VL |
|---|---|---|
| Males No 11-20 | 40 | 44 |
| Females No 1-10 | 36 | 35 |

Table 4 *Closest distance (LM) between ischial spine and ureter in 20 pairs of ureters*

| | Averages in mm |
|---|---|
| Males No 11-20 | 44 |
| Females No 1-10 | 30 |

AA was approximately the same in the two sexes, being 86 mm in the male and 83 mm in the female (see VB in fig 2)

From this latter relationship it became apparent that the course of the ureter from the pelvic brim down to the ureteral angle is practically the same in the male and in the female, a circumstance which indicates that the cause of the difference in length must be searched for in the part of the course from the angle to the bladder

Table 5 *Length (NN′) of 10 pairs of male and 10 pairs of female pelvic ureters (in mm )*

| Males | | Females | |
|---|---|---|---|
| Specimen | Ureter | Ureter | Specimen |
| 16 | 159 | 184 | 1 |
| 19 | 144 | 160 | 4 |
| 20 | 143 | 159 | 6 |
| 14 | 140 | 141 | 3 |
| 15 | 137 | 132 | 2 |
| 17 | 123 | 131 | 9 |
| 18 | 120 | 130 | 8 |
| 12 | 112 | 130 | 10 |
| 11 | 105 | 126 | 7 |
| 13 | 105 | 121 | 5 |
| Average | 129 | 141 | |

Table 6 *Distance of ureteral orifice from vertical (AA) and horizontal (BB′) reference lines (Averages in mm )*

| | Length of Ureter | Distance of Ureteral Orifice from Vertical Line NP | Distance of Ureteral Orifice from Horizontal Line NO |
|---|---|---|---|
| Males No 11–20 | 129 | 80 | −4 |
| Females No 1–10 | 141 | 63 | −26 |
| Difference | 12 | 17 | 22 |

Table 7 *Position of vesical orifice of urethra (S) relative to reference lines (ST and SU) and relative to symphysis pubis (GG′, SG′, and SG) (Averages in mm )*

| | Measurements from Film | | | | Direct Measurement | |
|---|---|---|---|---|---|---|
| | ST | SU | GG′ | SG′ | SG | NN′ |
| Males, 19 and 23 | 78 | 37 | 19 | 39 | 34 | 136 |
| Females, 21 and 22 | 61 | 50 | 12 | 23 | 25 | 146 |
| Differences | 17 | 13 | 7 | 16 | 9 | 10 |

Finally, it became apparent that the reason for the greater length of the female ureter is a slight, but permanent, difference in the position of the bladder, a difference too small to be apparent upon superficial inspection, but very evident if accurate measurements are made

Using the relationship of the vesical orifice of the ureters as a criterion for the location of the trigone, the distances of the ureteral orifices from the vertical and horizontal reference lines were measured They are recorded in table 6 (individual values in tables 1 and 2)

These measurements show that in the female the ureter ends farther ventrally and farther caudally than it does in the male, the female trigone, therefore, and with it the bladder, lies farther ventrally and caudally than the male trigone

These observations were further checked by ascertaining the relationship of the vesical orifice of the urethra in two males (No 19 and 23) and in two females (No 21 and 22), the results being listed in table 7

Relative to the reference lines AA and BB′, the urethral orifice (S) lies farther ventrally (ST) and farther caudally (SU) in the female than in the male We found also that the urethral orifice of the female (S) lies closer to the symphysis pubis (G) in both the vertical (GG′) and the transverse (SG′) plane Direct measurements in the cadaver (SG) agreed with the measurements taken from the films, the urethral orifice of the female was 9 mm closer to the inferior end *of the symphysis pubis in the female than in the male*

These figures show that in the female the bladder lies more ventrally and more caudally and closer to the symphysis pubis than it does in the male Moreover, the values of the differences pertaining to the bladder are approximately of the same order as the values of the difference in length of the ureter between males and females The conclusion is drawn that, on account of the difference in the position of the bladder, the ureter must travel about one half inch farther in ventrocaudal direction in the female than in the male

## SUMMARY

Summarizing all these observations, it may be stated that

The ischial spine is not a landmark in the course of the ureter since the ureteral angle lies about one and one-half inches away from the spine both cranially and ventrally, and since the ureter comes nowhere in its course near the ischial spine

The female pelvic ureter is approximately one half inch longer than the male pelvic ureter The cause of this difference is a difference in the position of the bladder In the female the bladder lies more ventrally and caudally and closer to the inferior end of the symphysis pubis than it does in the male

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# BETATRON THERAPY IN ADVANCED CARCINOMA OF THE URINARY BLADDER

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Advanced or sessile infiltrative carcinoma of the urinary bladder presents such a gloomy prognosis, both from a standpoint of curability and palliation that every available avenue of treatment must be fully explored. Our series of patients treated by betatron therapy for advanced carcinoma of the urinary bladder was undertaken on this basis. In every case treatment was instituted with the full realization that the ultimate outlook was very poor and that the possibility of cure was almost nil. No case was included in our series in which the possibility of radical cure by either surgical or conservative means was deemed possible. This approach is diametrically opposed to available information in the literature. Buschke, Cantril, and Parker,[1] who report one of the larger single series, point out that noninvasive papillary carcinoma of the bladder responded well to roentgen therapy, but that the intramural infiltrating portion of the carcinoma was not controlled and remained as a focus of recurrent disease. In Blomfield's[2] series, it was noted that the results became appreciably worse when radiation therapy was attempted on the more advanced cases. However, it was our belief that further clinical observation with perhaps an increased dosage was indicated in the more advanced and obviously hopeless cases.

The betatron has two principal advantages over the ordinary 200 KV radiotherapy machine. First, there is less "scatter" and therefore the area receiving maximum therapy can be better localized. Second, deeper penetration can be accomplished with a minimum of skin reaction and therefore a considerably greater tumor dose can be delivered to intrapelvic organs.

The betatron is a relatively new instrument in radiotherapy, therefore, reports in the literature are limited and usually cover a very short followup period. Mayor[3] reported 21 cases of which six were listed as improved 6 months to 2 years following therapy. He limited his treatment to those patients with deep cancers or with the carcinoma localized to the base of the bladder. Stapleton[4] who treated more superficial lesions reported fairly successful results. Of 18 cases, 8 were tumor-free after one year, 4 were dead, and 3 were still living with tumor. Only 2 cases of advanced carcinoma were treated and both patients died promptly. Blomfield,[2] with a 3-year followup, had 71 dead out of a total of 127 cases. Bus-

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Read at annual meeting, American Urological Association, Boston, Mass. May 28, 1956.

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chke, Cantril and Parker[1] presented 61 cases, 9 of which were well for 4 years, and 6 for 5 years There were 43 known dead out of the 61 Harvey, Hass, and Laughlin[5] presented 2 cases and both patients died early Hare et al [6] reported 29 cases with 13 free of disease, 7 dead, and 7 still living with tumor In summary, of all cases reported in the literature, there is approximately a 40 per cent survival over a 3-year period and in many instances the followup is for a much shorter time

From a survey of the literature a few general conclusions can be reached Betatron therapy is not successful in treating deeply infiltrating carcinoma of the bladder Poor results are obtained where treatment follows recent cystotomy Extensive low grade multiple papillomatosis is not improved Superficially infiltrative grade 2 and 3 lesions do respond to betatron therapy, but the ultimate overall survival rates are no better than those for transurethral or open surgical management

Our series consists of 17 cases, all with proven carcinoma of the urinary bladder Thirteen of these patients had transitional cell grade 3 or 4 lesions with muscle invasion, one had an advanced grade 2 lesion, two had epidermoid carcinoma, and one had adenocarcinoma Known pelvic node metastases, observed and confirmed by biopsy during a urinary diversion procedure, were present in one Four patients had urinary diversion into an ileal segment, two prior to treatment and two immediately after treatment

Originally, it was our impression from studies of the literature that the relative biologic effect of betatron therapy was 6 to 8 as compared to 200 KV radiation *Therefore, our patients were treated with large doses in order to compensate for* this lessened biologic effect Dosage varied from 4700 R to 7500 R given over a period of between 23 and 30 days, through 3 ports Further experience has led us to question the assumption that there is actually a reduced relative biologic effect

### PATHOLOGY

Accurate cystoscopic and microscopic followups were obtained at varying intervals following the completion of therapy on 10 patients *In 4 patients, there* was neither cystoscopic nor biopsy evidence of persistent tumor in the bladder In a fifth there was no cystoscopic evidence of recurrence, but deep biopsy from normal appearing bladder wall at the site of the previous tumor was not obtained Subsequent events namely, the development of a rectovesical fistula in one of the aforementioned patients would lead one to suspect that failure to demonstrate superficial tumor does not completely eliminate the possibility of residual carcinoma within the bladder wall Persistent tumor was found to be present in the bladder either by a biopsy or on postmortem examination if 4 cases and was also

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TABLE 1

| Name | Grade | Dosage R days | Alive | Dead | Cause of Death | Biopsy After Treatment | Complications |
|---|---|---|---|---|---|---|---|
| M | Gr 3-4 | 7500-38 | | 2 mo | Extensive multiple metastases | | Mild diarrhea |
| W | Pos pelvic nodes—Gr 4 | 7500-39 | | 1½ yr | Multiple metastases Bladder showed no carcinoma at autopsy Nodes not sterilized | | Had repeated diarrhea Severe rectocolitis Urinary diversion to ileal loop Bilateral hydronephrosis |
| K | Gr 3 Sessile | 7200-27 | | 9 mo | Multiple metastases | No tumor in bladder after 3 months | No gastrointestinal complaints |
| C | Extensive Gr 4 Sessile | 6000-29 | | 12 mo | Metastases, rectovesical fistula | No tumor in bladder after 4 months | Severe diarrhea during treatment Asymptomatic for 9 months |
| S | Tr cell Gr 3 | 6780-41 | 14 mo | | | No tumor—6 mo | Intractable radiation cystitis Ileal bladder substitution—Colostomy Intestinal obstruct Transverse colostomy |
| W | Gr 4 Sessile | 7700-44 | 14 mo | | | | After 10 mos one tiny crater, looked like carcinoma Gross hematuria had ceased, excellent relief of symptoms Now has progressive local recurrence |
| S | Gr 3 Tr cell | 6600-42 | | 8 mo | Carcinoma still present in bladder Bowel perforation | | Ileal bladder prior to Rx Subphrenic and subdiaphragmatic abscess, terminal |
| R | Tr Gr 3, recurrent | 7600-49 | 14 mo | | | | 11 mos No cystoscopic evidence of tumor Treated by surgery for intestinal obstruction |
| M | Gr 2 Tr cell | 5860-38 | | 1 mo | General debility Probable peritonitis | | Marked gastrointestinal symptoms |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| H | Gr 3 Tr cell | 7000–39 | | 5 mo | No gross tumor No cancer in extravesical mass | | Moderate diarrhea Probably died of intestinal perforation |
| K | Epidermoid Chr inflam | 5600–31 | | 1½ mo | Perforated bladder | | Severe E coli infection |
| F | Gr 4 Large tumor | 5000–23 | | 6 mo | Unknown | | Severe urgency Ileal segment at end of therapy |
| P | Epidermoid carcinoma | 5500–30 | | 6 mo | Unknown | | |
| B | Adenocarcinoma | 6500–37 | | 7 mo | Residual carcinoma in bladder | | Moderate diarrhea and cystitis Large bowel obstruction Colostomy Cutaneo rectoileocecal fistula |
| F | Gr 3 Tr cell | 6600–37 | | 3 mo | Coronary occlusion | | Excellent relief of symptoms |
| M | Gr 3 Muscle | 4700–30 | | 2 wk | | | Suicide |
| S | Partial cystectomy Gr 3 Tr | 5200–30 | 5 mo | | | | Originally had retroperitoneal metastases with edema of leg Regression of mass but now has recurrence in upper abdomen |

noted cystoscopically in one patient in whom no biopsy was obtained All biopsy and postmortem bladder specimens showed definite radiation effect

## COMPLICATIONS

*Immediate mortality* Two patients died almost immediately upon conclusion of therapy Both of these patients had advanced general debility prior to the institution of therapy The exact cause of death in one was not determined, but it was our clinical impression that he probably had generalized peritonitis The second exhibited profound shock of sudden onset and at autopsy was found to have experienced a spontaneous perforation of the bladder

It is our definite opinion that betatron therapy should not be administered to patients with advanced cachexia During the course of therapy in almost every instance there was some general systemic deterioration In most instances this was temporary, but in some instances was sufficiently severe to necessitate hospitalization and temporary discontinuance of the therapy Although one may encounter an occasional patient who tolerates a course of treatment far better than was anticipated, this form of treatment should not be utilized in patients in poor general physical condition

*Urinary symptoms* Since many of our patients presented marked urinary frequency, urgency, and nocturia prior to treatment, it is difficult to differentiate symptomatology produced by the radiation effect from that produced by the tumor or a superimposed infection Two of our patients had urinary diversion prior to the institution of therapy Nine patients suffered only mild irritative symptoms, two were listed as moderately severe, and four had severe frequency, urgency, and burning, two of sufficient severity to require subsequent urinary diversion In many instances an excellent degree of palliation was obtained in patients with severe urinary symptoms prior to the institution of therapy In five of these patients, all of whom were exhibiting marked irritative phenomena and recurrent hematuria, there was a complete subsidence of local symptoms with the development of an adequate bladder capacity Transurethral biopsy in two patients relatively free of urinary symptoms showed a surprising amount of radiation reaction One must consider the possibility that delayed radiation reaction may have occurred in these individuals, however, it is our impression that the delayed radiation reaction is more apt to occur after radium implantation than following external radiation therapy

*Gastrointestinal complications* All patients experienced moderately severe intestinal cramps and diarrhea beginning about the third week of treatment and persisting for 2 weeks after completion

The principal major complication which we have encountered in our series has consisted of intestinal obstruction and/or perforation Nine of the 17 patients have presented major gastrointestinal complications, the commonest being intestinal obstruction Obstruction was accompanied by perforation in three instances Surgical intervention was required in 6 cases In 1 patient a rectovesical fistula developed, in two a severe rectocolitis with intractable diarrhea developed

An analysis of the current betatron literature fails to reveal any incidence of gastrointestinal complications comparable to ours The development of this severe complication may have been the result of a calculated risk It was definitely our feeling that the main advantage of this type of therapy was the possibility of salvaging those cases in which the tumor had extended beyond the possibility of radical surgical removal Therefore, it was obvious that a cancerocidal dose had to be delivered, not only to the bladder itself, but to the entire pelvic area and lower abdomen Unquestionably gastrointestinal complications could have been minimized by a reduction of the number of fields and a reduced dosage However, some complications are inevitable even with the utilization of a palliative dose Furthermore, such a reduction in treatment would have eliminated any hope of cure in that group in which the most benefit might have been gained Unfortunately these assumptions were not confirmed and our experience has been such that we now believe that advanced carcinoma of the urinary bladder with extension is incurable by any means and that radiotherapy should probably be limited to palliation in such cases

### ULTIMATE SURVIVAL

Only 4 patients of our series are alive One of these patients has a transverse colostomy and the urine has been diverted into an isolated ileal segment He is some 14 months' after treatment, has gained weight, and his general condition is satisfactory As far as we have been able to determine, cystoscopically and by bladder biopsy, he is free of carcinoma A second, also surviving 14 months, has experienced an intestinal obstruction requiring surgical correction but at the present time is doing satisfactorily and there is no cystoscopic evidence of carcinoma in the bladder He is completely asymptomatic as far as the urinary tract is concerned Two are alive with definite evidence of persistent carcinoma One of these two has had excellent palliation There was a marked regression of his tumor cystoscopically, but recently after approximately one year, the tumor has begun to grow and the patient is now experiencing an occasional episode of gross hematuria Thirteen have expired, the longest survival being 13 months, the average being about 3 months Two patients in whom there was apparently complete cure of the bladder carcinoma died of multiple metastases, one at the end of 9 months and the other after 12 months

### DISCUSSION

Although our series is comparatively small, I believe that some definite conclusions can be drawn from it We have confirmed the impression of others that the possibility of curing otherwise hopeless cancer of the bladder by betatron therapy is not feasible With possibly two exceptions, it is perfectly evident that we have not prolonged the life of any of these patients Furthermore the considerable number of gastrointestinal complications and the definite systemic depression in some have actually been contributory factors in shortening their ultimate survival

On the positive side of the ledger has been excellent palliation in 7 cases as far as bladder symptoms are concerned In 5 cases the primary lesion has been destroyed, indicating that some of these tumors are radiosensitive and that the betatron is capable of delivering a sufficient dose to accomplish this destruction The possibility of a favorable response in superficially invasive tumors must be kept in mind Although it is much too soon to evaluate, in at least one instance the possibility of our having eliminated the primary disease in an advanced case is a good one

It is still our impression that radical surgery presents the best possibility of cure in patients with lesions localized to the urinary bladder, if the patient is a suitable surgical risk Betatron therapy should be utilized as a palliative instrument in inoperable cases, but the treatment should be directed at the bladder alone, no effort being made to attack the areas of lymph node drainage The betatron is of value in the management of grades 3 and 4 sessile vesical carcinoma, not too advanced, in which surgery is contraindicated for constitutional reasons It should also be used as a curative instrument in patients who refuse radical surgery

## SUMMARY

Seventeen cases of advanced carcinoma of the urinary bladder treated by betatron therapy are presented From this group, there are four survivors, two of whom have persistent carcinoma

An extremely high incidence of major gastrointestinal complications was encountered

Good palliation of bladder symptoms with disappearance of the primary tumor was obtained in several cases

The use of the betatron as a curative agent for advanced carcinoma is not recommended

Betatron therapy is of value in earlier cases where surgery is contraindicated, or in patients who refuse surgical intervention

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# OSTEOGENIC SARCOMA AND TRANSITIONAL CELL CARCINOMA OCCURRING SIMULTANEOUSLY IN THE URINARY BLADDER

## REPORT OF A CASE

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Osteogenic sarcoma of the bladder is extremely rare The occurrence of such a tumor in association with a transitional cell carcinoma is even more unusual

Three hundred twenty four vesical sarcomas of all types have been recorded since the initial report by Deschamps[1] in 1791 Many histologic varieties have been described (table 1) among which were 11 tumors producing bone or cartilage[2] [3] [4] Of these 324 recorded sarcomas, 17 have coexisted with a carcinoma The following case is an example of this most unusual type of tumor occurring in the urinary bladder

### REPORT OF A CASE

C B , a 79 year-old retired chair maker, was admitted to the Mary Imogene Bassett Hospital on February 7, 1955, complaining of urinary frequency, dysuria and hematuria of 4 weeks' duration

Forty years prior to the present illness the patient contracted gonorrhea, 30 years later he was treated successfully for a urethral stricture and benign prostatic hypertrophy by repeated urethral dilatations and transurethral prostatic resection Five years prior to admission the patient again suffered frequency, dysuria, hematuria and some incontinence At this time cystoscopic and laboratory examinations disclosed only cystitis which responded to chemotherapy and antibiotics

In his later years he had suffered from chronic bronchitis, pulmonary emphysema, arteriosclerotic heart disease with hypertension, occasional episodes of mild congestive failure, and anginal pain Treatment had consisted of digitalis, potassium iodide, and oral mercurial diuretics

Four weeks prior to admission frequency dysuria, hematuria and nocturia recurred Chlortetracycline was administered by the family physician with partial relief of symptoms and he was referred to the Hospital for further investigation and treatment

The pulse rate and respiratory rate were normal, the temperature was 100 4F

The patient was a well-developed and fairly well nourished white man in no distress The fundic vessels were moderately tortuous The anteroposterior diame

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To explain the formation of bone in rare cases, several investigations are pertinent Neuhof[6] in 1917 showed that bone formed invariably in fascial transplants placed in the bladder That the fascia itself was not responsible was verified by the observance of osteogenesis in fat transplants also He believed that this change in cellular structures represented connective tissue metaplasia, stimulated by calcium salts derived from the urine In 1931, Huggins[7] investigated the formation of bone under the influence of epithelia of the urinary tract and discovered that transplants of vesical, ureteral, and renal epithelium to certain parietal fascias and muscle, and to synovial membrane in dogs led to osteogenesis In the cysts resulting from such transplants, the fluid was found in many cases to have a higher content of calcium and phosphorus than serum Entz[8] also has shown that vesical mucosa normally secretes calcium and phosphorus These elements must, of course, be present for the formation of bone That urine is not necessary in the process, has been verified by Huggins[7] who diverted the urinary stream, repeated the fascial transplants of Neuhof, and learned that bone still formed in the transplants within the functionless bladder

More recently investigation has turned to the enzymes necessary for osteogenesis Kabat and Furth[9] studied the phosphatase in normal and neoplastic tissues and found that the epithelium of the renal pelvis and the urinary bladder of a mouse embryo gave a strong reaction for alkaline phosphatase Other animals were not examined This enzyme was also present in the normal epithelium of the small intestine However, Huggins[7] has shown that epithelial transplants of small intestine to fascia do not result in bone-formation as do transplants of epithelium from the urinary tract Thus it is apparent that another of the factors necessary for osteogenesis is present in the epithelium of the bladder

In the case here reported, the added presence of a papillary transitional cell carcinoma is of interest Saphir and Vass[10] expressed the opinion that such tumors might represent simply transitional cell carcinomas with anaplastic features Virchow[11] believed that "within the primary carcinomatous or sarcomatous elements, the stromal or epithelial portions respectively were subsequently or simultaneously stimulated to malignant growth " The nature of this "stimulation" is not known

In general, sarcomas of the bladder occur in the very young or after the age of forty-five The most frequent location is at the trigone They grow rapidly, metastasizing in 25 per cent of the cases The mortality is extremely high and where the general condition of the patient permits, cystectomy offers the best therapy

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## SUMMARY

An unusual case of osteogenic sarcoma and transitional cell carcinoma occurring simultaneously in the urinary bladder is herewith reported

The potential osteogenic activity of urinary epithelium, the ability of the vesical mucosa to secrete calcium and phosphorus, and the presence of alkaline phosphatase in the epithelium of the bladder may be responsible for the rare formation of bone and cartilage in an occasional sarcoma of the bladder

The coexistence of such a tumor with a transitional cell carcinoma may be the result of simple anaplasia alone or may be due to some unknown factor "stimulating portions of the primary lesion to malignant change"

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# THE RELATIONSHIP BETWEEN URETHRAL RESISTANCE AND CHRONIC URINARY TRACT DISEASE IN WOMEN

DAVID M DAVIS

Contracture of the vesical orifice is no newcomer in the urological field, but its frequent occurrence and serious effects are still being appreciated more and more each year More than three quarters of a century ago Guthrie of England recognized that urinary obstruction could exist in men whose prostates were not enlarged, and devised an incisor with a snow-plow like action to slit open the vesical orifice Mercier of France made similar observations, interpreting the pathological change as a bar or dam extending across the posterior aspect of the vesical orifice—still spoken of as Mercier's bar Other French authors proposed the term *prostatisme sans prostate*, meaning obstruction without enlargement of the prostate gland Mercier in his turn invented a median bar excisor, designed to remove a piece from the bar, and the forerunner of Young's well known punch instrument and of the Bumpus and Thompson prostatic resectors Only slowly has it been realized that the obstruction is not always due to a posterior bar, and that circumferential contractures are common and produce effects indistinguishable from those of the so-called median bar

These conclusions are part and parcel of greatly increased knowledge of the whole physiology and pathology of the lower urinary tract It seems to me that the different items of this increased knowledge fit together into a reasonable, understandable picture which explains a great deal about urinary tract disease in general and lower urinary tract disease in particular Cystometric studies have shown what the normal intravesical voiding pressure is This pressure forces the urine out through the urethra against the urethral resistance, whatever that may be, and under normal circumstances produces a rate of flow through the urethra which empties the bladder completely before muscle fatigue terminates the contraction of the detrusor muscle This fatigue may occur within 20 to 25 seconds If we assume empirically that the maximum bladder capacity in an adult is 500 cc, the rate of flow through the urethra would have to be from 20 to 25 cc per second to fulfill the above requirements Dr Willard Drake has concluded, from studies with his ingenious uroflow meter that the average rate of flow in a group or several hundred presumably normal young adults (medical students) is 22 cc per second

Urethral resistance depends for the most part upon the caliber of the narrowest point in the urethra (which includes of course the vesical orifice) One should mention considerations of angulation, variation in caliber, character of the internal surface of the urethra, turbulence, and so forth, which may in the future be shown to have an appreciable influence As urethral resistance increases, the detrusor muscle hypertrophies, increasing the intravesical voiding pressure This in turn increases the velocity of the flow of urine at the narrowest point in the

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Read at annual meeting, Mid-Atlantic Section of American Urological Association, Hot Springs, Va April 21, 1956 urethra, thus keeping the actual voiding time within normal limits This compensation, however, is obtained at the cost of an increased intravesical voiding pressure, and decades of clinical observation attest that this may bring about serious and quite varied effects

W R Stevens of San Francisco, at least as long ago as 1923, published observations of bladder infections in women which were marked by very noteworthy originality He designed an ingenious and delicate instrument with which he found that if the female urethra calibrated less than 28F the patient was very likely to be subject to chronic or recurrent bladder infection, while if it calibrated larger than No 28, the patient was practically certain to be free of such infections In spite of the fact that Frank Hinman clearly and thoroughly systematized the entire concept of the relation between obstruction and infection in the urinary tract and that a certain small number of urologists, of whom one recalls particularly the late Alfred I Folsom of Dallas followed in the footsteps of Stevens with the most gratifying success, the whole idea of the importance of urethral obstruction in the bladder infections of women has been accepted slowly and apparently reluctantly not only by the medical profession generally but also by many urologists Such infections are, as we all know, extremely common and this is the reason I have designated contracture of the vesical orifice, frequently present in both sexes as a neglected lesion

In discussing this aspect of urinary tract disease, I should like to refer to a series of 169 of my own private cases, all females, from whom answers to a questionnaire have been received *I hope that these statistics will show that the* principles of diagnosis and treatment are well established but I believe that they will also show that certain technical problems of treatment are still far from solved

The symptoms produced by urethral obstruction in women may be the classical symptoms of lower urinary tract obstruction, namely frequency, hesitancy urgency, straining, small weak stream, interruption and pain on voiding In other cases the symptom picture is more confusing, including the following items suprapubic (bladder) pain, renal pain, unilateral or bilateral, digestive disturbances, and chronic or recurrent bladder infections, which may spread to the kidneys in the acute phase Since the introduction of modern antibiotic drugs, one often hears a history of continuous voiding symptoms of slight or moderate degree, punctuated by episodes of acute cystitis yielding quickly to medication but never failing to recur after a time It is unfortunate that this clinical picture has come to be regarded by many physicians as hopeless from the point of view of treatment As a result of this attitude, many patients have become discouraged or fatalistic, and no longer seek treatment This is a tragedy, as it leads to much chronic ill health, and eventually to serious kidney damage Successful methods of treatment would benefit untold thousands of women

In the diagnosis, the history usually gives the clue, if carefully taken with all questions pressed persistently home The physician should insist that frequency should never be ignored or made light of If marked voiding symptoms are present with a clear sterile urine one looks confidently for an obstructive

lesion Cystoscopic examination may show muscular h
and cellules but often does not At the orifice a right
nothing, but a careful study with retrospective and f
close the small size of the orifice, and in the urethra
congested and edematous mucosa and polyp formation
meatus is easily seen, and calibrated with suitable inst
bration serves to detect strictures of the urethra pro
whether the expulsive force is normal, decreased or in
arranged commode chair, uroflowmetry can be carried
A single urethral dilatation at the time of the first vi
test and may be very illuminating if it brings about a n
even though temporary It should be said that in al
primary upper urinary tract disease has been ruled ou

Systematic urethral dilatation, including eventual o
sizes such as 42 or even 45F is curative in a great many
in more resistant cases include electrocoagulation of
urethral meatotomy, internal urethrotomy, and enl
orifice by transurethral resection These procedures of
cures, but not invariably, which forces one to believe th
needed as to when to apply the various surgical measu
carry them to be sure they are adequate to produce th

Classification of results in my series has been somewh
of the most thoroughly pleased and satisfied patients
returned completely to a normal state If however, the sy
tions no longer occur, and satisfaction of the patient is
have been included with the complete cures as satisfa
in table 1 There are are 90 such cases, or 53 2 per cent o
13 6 per cent of the total, are doing very well, but find t
a single dilatation at certain intervals to avoid recurr
one may say that 113 cases, 66 9 per cent of the total h
fully

TABLE 1

Well, or fully satisfied with present status

| | | |
|---|---|---|
| 10 years or more | 12 | 3–5 years |
| 8–10 years | 6 | 2–3 years |
| 5–8 years | 14 | 1–2 years |

TABLE 2

| | |
|---|---|
| Improved | |
| a Under treatment some regular some irregular some advised to have T U R | 5 |
| b Going along on improved status without treatment some almost well some with still a good many symptoms | 20 |
| c After a well period recurrence of original symptoms | |
| α Undergoing further treatment | 6 |
| β Under treatment by other doctors | 4 |
| γ Without further treatment | 4 |
| δ Dilatations continued for hypertension | 1 |
| Total improved | 40 |

Table 2 shows the cases which are definitely improved, but which cannot be called well or entirely satisfactory Five come regularly or irregularly for dilatation, not always avoiding recurrences of infection Three of these have been advised to undergo transurethral resection, but hesitate to do so Twenty are improved enough so that they have ceased treatment Some are almost well enough to be included in the "satisfactory" category in Table 1, others are far from well, but so much better than formerly that they are thankful Fifteen had results which were extremely satisfactory, but have suffered recurrences of the original symptoms after varying periods without treatment, ranging from 8 months to 7 years Six of these are undergoing further treatment at my hands four have consulted other urologists, four are fighting it out without further treatment, and *one is a very special case This patient has no voiding symptoms* or infections but if regularly spaced dilatations are omitted, the blood pressure rises, sometimes as high as 190 mm of Mercury The improved cases number 40 or 23 7 per cent of the total

Table 3 shows the unimproved cases In one the diagnosis must have been incorrect, as the patient reports that she is completely free of symptoms after removal of an ovarian cyst Two sought treatment with other urologists one at her own instance, the other at mine Twelve received treatment considered inadequate, and did not return for various reasons Some were deterred by distance, some by financial considerations some by intercurrent non urinary disease, and several found the treatments too painful at the time or later In one neurotic patient I was completely confused by the patient's contradictory statements The number unimproved is 16 or 9 5 per cent of the total

As to the methods of treatment 54 patients underwent electrocoagulation of the urethra one or more times Transurethral resection of the vesical orifice was performed in 40 patients in one of them twice Eight meatotomies are recorded, but I am sure this was done in a number of other cases In practically all of the aforementioned cases urethral dilatation was carried out before or after the operative procedure or both before and after All of the remaining cases were treated by urethral dilatation only Dilatation was usually begun with sounds, and continued with the Kollmann dilator, which enables one to go as high as number 45 French, which represents a diameter of 15 millimeters It frequently happens

TABLE 3

| | | |
|---|---|---|
| Not improved | | |
| a | Wrong diagnosis well after removal of ovarian cyst | 1 |
| b | Sought treatment elsewhere | 2 |
| c | Inadequate treatment, did not return, (some found treatment too painful) | 11 |
| d | Neuro-psychiatric status, result hard to evaluate | 1 |
| | Total unimproved | 16 |
| | Total cases, unimproved, improved and well | 169 |

that in cases responding very satisfactorily to dilatation no noteworthy improvement is noted until the dilatation reaches above size 35, sometimes even 38 or 40 Such dilatations are painful, but if effective local anesthesia is used the duration of discomfort is short, and, unless symptomatic improvement is such that the patient considers the discomfort well worth while, this form of treatment should be quickly discontinued

My objects in writing this paper are two, namely, first, to present the evidence I have to show that obstruction, at the vesical orifice or in the urethra, is the underlying cause of most chronic and recurrent cystitis, and second, to point out the need for attention to the treatment of this underlying lesion with the object of improving its technical aspects

I consider the first objective to be of extreme importance, since there is so little recognition in the medical profession generally of the relation of obstruction to infection, or of the fact that the obstruction can be very slight and still have its dire effects This is well illustrated by the following quotation from an article entitled "Management of Infections of the Urinary Tract"—splendid from the point of view of drug therapy—by Edward H Kass of Boston (Am J Med , **18** 764, 1955) "Our present state of knowledge is so incomplete that a high percentage of failure in certain types of infection will characterize therapeutic activity until more fundamental knowledge concerning infections of the urinary tract has been accumulated " I submit that there is a great deal of such fundamental knowledge easily available in the literature of urology, and in the experience of urologists It is a pity that internists and urologists do not establish more fruitful collaboration in this matter, and it is devoutly to be wished that such collaboration will take place abundantly in the future

There are two observations I should particularly like to make in regard to the therapeutic problem The first is that all of the methods presently available are, in many individuals, painful to such a degree that their usefulness is often compromised thereby Anesthesia is not the answer, since the worst discomfort is often in the post-treatment period A means of minimizing this discomfort is most urgently needed The second observation derives from the fact that in a good many cases transurethral resection or even thorough dilatation will bring about a cure so prompt, so complete and so permanent that the patient regards it as almost miraculous, while in other cases, where the treatment is carried out just as conscientiously and with just as much effort to make it thorough, either the result falls short of being satisfactory, or, after a period of complete relief, the original trouble returns In females, the fear of causing extravasation exerts a constant pressure on the urologist toward conservatism, and this is no doubt the cause of many not quite adequate resections The fear of causing incontinence may prevent adequate internal urethrotomy and dilatation It will be, therefore, the task of some one to discover criteria for the adequacy of these operations comparable to those we have for them in the male sex When this task is completed I am confident that the treatment of urinary tract infection in women already so much improved, will very probably approach as near to infallibility as we may hope for in the practice of medicine

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# THE RESEMBLANCE OF HYPERTROPHY OF THE PROSTATE TO CONGENITAL POLYCYSTIC DISEASE RECONSTRUCTION OF CYSTIC LESIONS OF HYPERTROPHIED PROSTATE IN THREE CASES

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Some years ago the senior author, while studying the pathogenesis of polycystic disease of the newborn, was impressed by the similarity of the lesions of this disease with those of so-called benign hypertrophy of the prostate Although there is not an obvious relationship between the etiologies of the two diseases, it is believed that the anatomical similarities are worth recording since the detachment of dilated prostatic acini as isolated cysts has not been previously emphasized as a feature of hypertrophy of the prostate

## MATERIALS AND METHODS

Case 1 (autopsy No 49-146) was a Negro, aged 49, who died of hypertensive heart disease and uremia due to chronic pyelonephritis Additional findings included widespread chronic passive congestion and non-suppurative pericarditis and pleurisy Case 2 (autopsy No 49-145) was a white man, aged 76, who died of cerebral hemorrhage incident to arterial hypertension and arteriosclerosis Case 3 (autopsy No 51-78) was a white man, aged 80, who died of arteriosclerotic heart disease complicated by old and recent myocardial infarctions

At autopsy all tissues were fixed in a 10 per cent formalin solution Blocks were embedded in paraffin and sections were stained with Delafield's hematoxylin and eosin In each case, two cubical blocks about 1 5 cm on a side were cut from the periphery of a lateral lobe and from the mesial aspect of the same lobe so as to include the floor of the urethra lateral to the verumontanum Several hundred serial sections, 10 micra in thickness, were cut from each block in a plane approximately at right angles to the long axis of the prostatic ducts and acini Hyperplasia of the stroma and abnormalities of ducts and acini were traced and studied in these sections Representative segments of each each block were reconstructed by the method previously described[1] [2]

*Case 1* Gross examination The prostate, which measured 4 cm in diameter, was only slightly enlarged (fig 1) No distinct nodules of hyperplasia were seen, but the stroma of the lateral lobes appeared to be more fibrous than normal In small areas lateral and posterior to the urethra, the acini were dilated to form minute cystic structures

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[1] Norris, R F and Herman, L Observations on the anatomic basis of congenital polycystic kidneys Tr Am A Genito-Urin Surg , 31 41–57, 1938

[2] Norris, R F and Herman, L The pathogenesis of polycystic kidneys reconstruction of cystic elements in four cases J Urol , 46 147–176, 1941

Microscopic examination Beneath the urethra the fibromuscular stroma appeared to be increased in amount The larger ducts however, did not appear to be generally compressed (fig 2, 1) Between this area and the periphery of the lateral lobes some of the acini were dilated and cystic, but in the periphery of the lobe the acini were not dilated (fig 2 *B*) Corpora amylacea were numerous

Reconstruction When traced in serial sections, the ducts emptying into the urethra were relatively uniform and normal in appearance The acini in this area also appeared normal (fig 3, *A*) Reconstruction of a group of acini near the periphery of the lateral lobe showed a slight uniform dilatation of most of them, but the configuration was not generally disturbed (fig 3, *B*)

*Case 2* Gross examination The prostate measured 6 cm in greatest diameter and was enlarged as the result of nodular fibrous and glandular hyperplasia which distorted the normal structure (fig 4) The verumontanum was almost obliterated

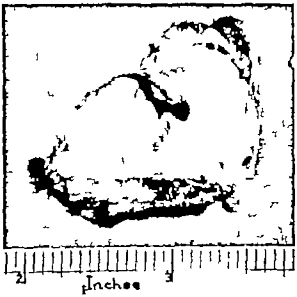

FIG 1 Case 1 Cross-section of prostate Size approximately normal Patchy cystic dilatation of acini is beginning in lateral lobes among bands of fibrous hyperplasia

Microscopic examination The ducts emptying into the urethra were surrounded by dense fibromuscular stroma which appeared to have compressed the ducts in some areas (fig 5, *A*) and to have allowed dilatation of the ducts in other localities Corpora amylacea were numerous In the lateral areas of the gland the acini were often dilated into multiloculated structures lined by single layers of flattened epithelium or by papillary projections of epithelium which had the appearance of recent proliferative activity (fig 5, *B*)

Reconstruction In serial sections and reconstructions the prostatic ducts and acini near the urethra were irregularly dilated and the junctions of the acini with the ducts were often narrow and constricted Isolated cysts in this region were not observed (fig 6) At the periphery of the gland however, there were numerous large cysts composed of enlarged coalesced prostatic acini which ended blindly in all directions Because of the complexity of the cystic dilatations it was not determined how many peripheral acini still communicated with the prostatic ducts (fig 7)

*Case 3* Gross examination The prostate which measured 5 cm in greatest

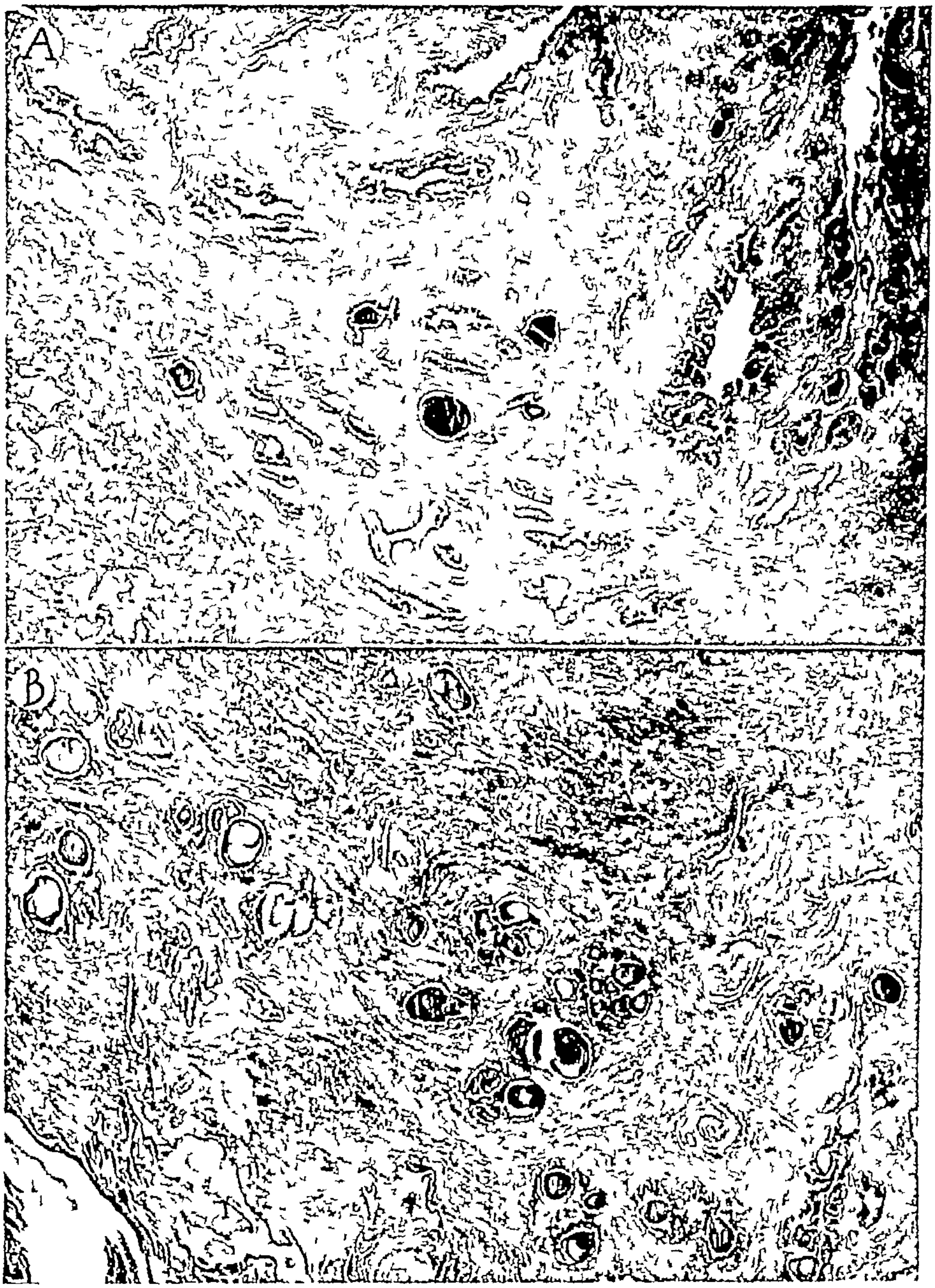

Fig 2 Case 1 *A*, photomicrograph of prostate tissue near posterior urethra shows increased density of fibromuscular stroma and only slight proliferation of ducts *B*, photomicrograph of prostatic tissue of lateral lobe near capsule also shows slight fibromuscular hyperplasia without dilatation of acini ×30

diameter was enlarged as the result of nodular fibromuscular hyperplasia Enlarged acini were scarcely visible to the unaided eye The fibrous nodules appeared to have originated predominantly in the so-called lateral lobes The posterior urethra in the plane of the verumontanum was compressed by the nodules (fig 8)

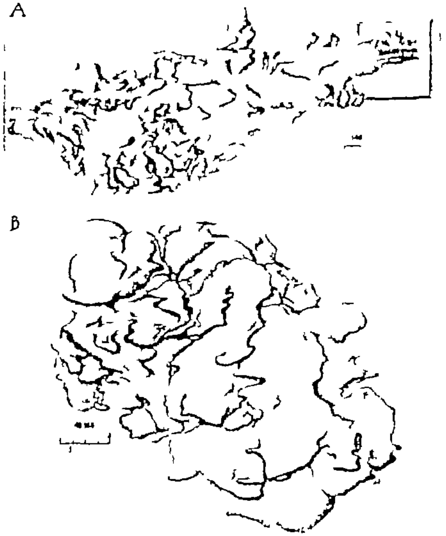

Fig 3 Case 1 *A*, prostatic acini and duct emptying into urethra Reconstruction shows *only slight irregularity and dilatation There are no isolated segments One inch on scale* equals 100 microns in tissue *B* prostatic acini in lateral lobe near capsule Reconstruction shows slight uniform dilatation of acini but no isolated segments One inch on scale equals 100 *microns in tissue*

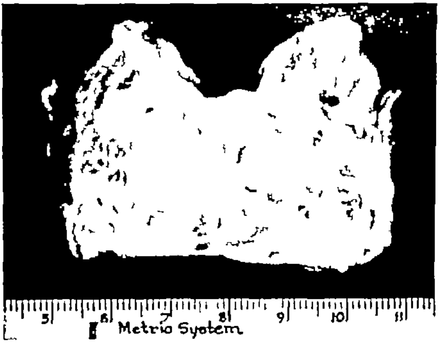

Fig 4 Case 2 Cross section of prostate Prostate is enlarged as result of extensive fibromuscular and glandular hyperplasia of lateral lobe

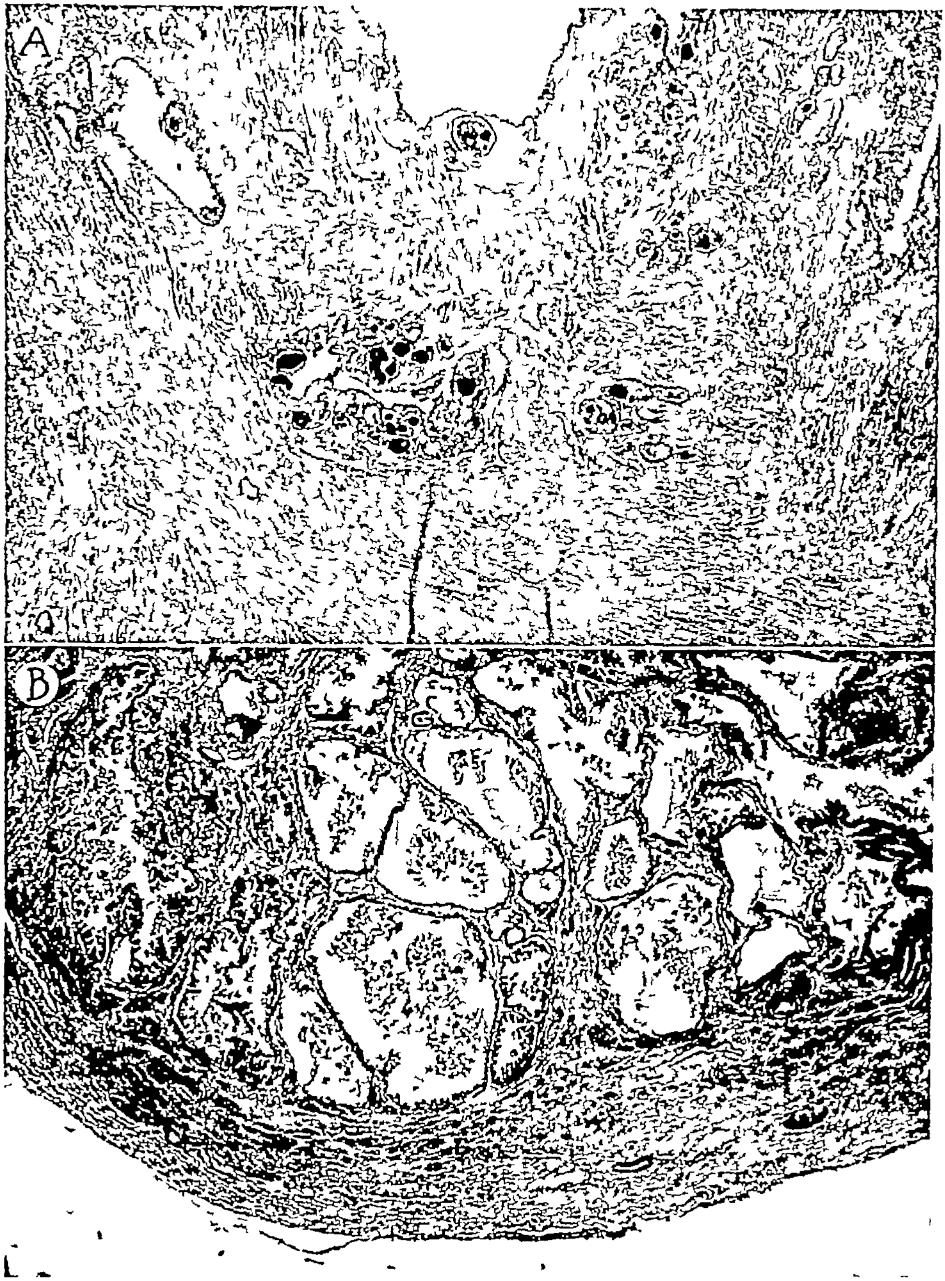

FIG 5 Case 2 A, photomicrograph of prostate tissue beneath the urethra seen in upper portion of picture Ducts are surrounded by stroma showing fibromuscular hyperplasia *B*, Photomicrograph of prostate tissue beneath capsule Acini are uniformly distended and anastomoses between acini appear to have resulted from rupture of septa ×25

Microscopic examination The prostatic ducts and acini close to the urethra were narrowed or occluded by squamous metaplasia Many of the acini contained corpora amylacea (fig 9, *A*) Between the periurethral region and the periphery of the prostate, the lobular structure was destroyed by fibromuscular hyperplasia

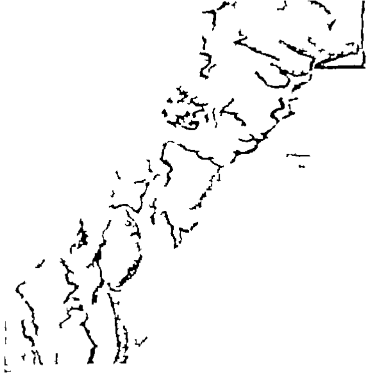

Fig 6 Case 2 Prostatic acini and a duct emptying into urethra Reconstruction shows irregular cystic dilatation of duct and acini One inch on scale equals 100 microns in tissue

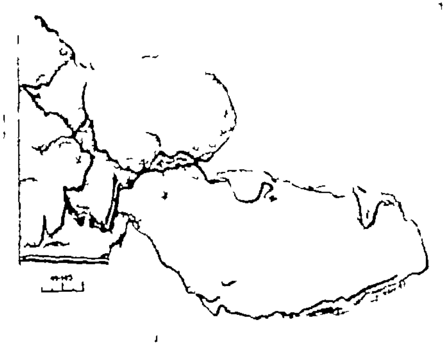

Fig 7 Case 2 Prostatic acini of lateral lobe near capsule Cystic dilatation of acini is marked In lower center is a large anastomosed group of acini which is completely ioslated as a cyst One inch on scale equals 100 microns in tissue

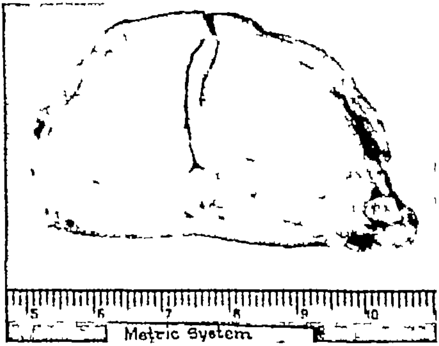

Fig 8 Case 3 Cross section of prostate Moderate enlargement is due to preponderance of fibromuscular hyperplasia over glandular hyperplasia

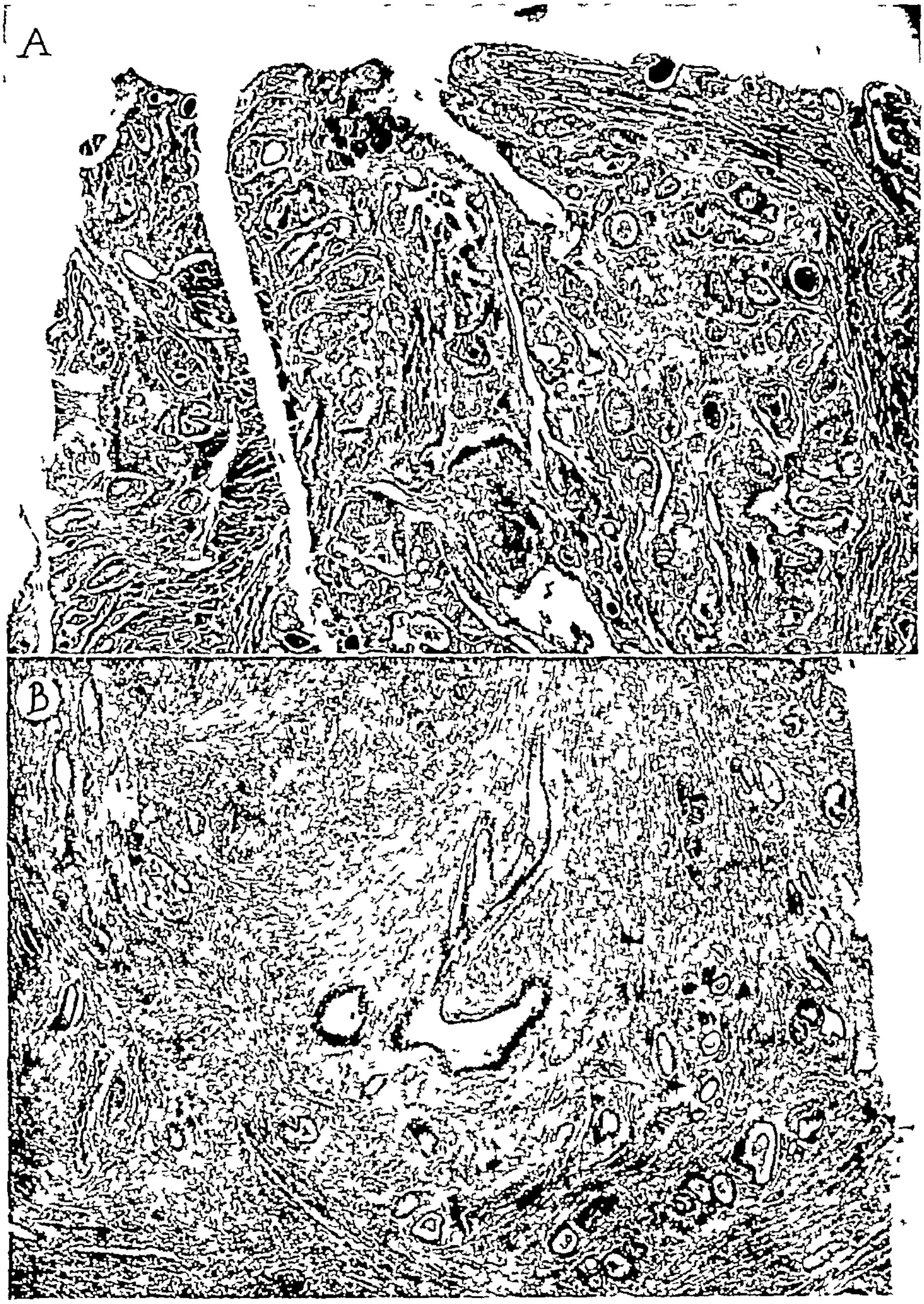

Fig 9 Case 3 *A*, photomicrograph of prostatic tissue beneath urethra seen in upper portion of picture There is little fibromuscular hyperplasia in this region Squamous metaplasia of ducts is apparent ×25 *B*, photomicrograph of prostatic tissue of lateral lobe near capsule Fibromuscular hyperplasia of stroma is evident Some acini are irregularly dilated but others are small and atrophic ×30

of the stroma Many of the acini and ducts were small and atrophic Others embedded in bundles of muscle and connective tissue were irregularly enlarged and distorted (fig 9, *B*)

Reconstruction In reconstructions made from serial sections, the irregularity

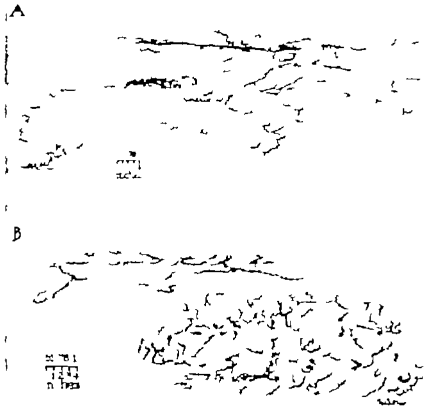

FIG 10 Case 3 *A* prostatic acini and ducts emptying into urethra Reconstruction shows that ducts and acini are irregularly dilated and some are anastomosed One complex of intercommunicating acini is isolated as a cyst in mid portion of illustration One inch on scale equals 100 microns in tissue *B* prostatic acini in lateral lobe near capsule Reconstruction shows moderate proliferation of acini which has resulted in dilatation and anastomoses between them An isolated cystic complex is shown in lower mid portion of illustration One inch on scale equals 100 microns in tissue

in size and shape of the ducts and acini was demonstrated both in the areas near the urethra (fig 10 *A*) and in the region beneath the capsule (fig 10, *B*) In both areas, segments of ducts and acini were segregated as isolated cysts which did not communicate with other epithelial structures

## COMMENT

Case 1 was selected for study since the prostate was considered typical of a man in early middle age The areas of glandular enlargement were localized and not extensive In the serial sections studied none of the enlarged glands were seen to be isolated as cysts Case 2 was selected since the prostate showed a preponderance of glandular hyperplasia and case 3 a preponderance of fibromuscular hyperplasia Neither gland was unduly enlarged Greatly hypertrophied prostates were not chosen for study because it was feared that the first changes in structure might be obscured in advanced stages of the disease

## DISCUSSION

In the case of polycystic disease of the newborn, evidence has been presented previously by the senior author and his collaborators[3-5] that the embryological

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[3] Norris R F and Tyson R M The pathogenesis of polycystic livers Reconstruction of cystic elements in two cases Am J Path 23 201-215 1947

[4] Norris R F and Tyson R M The pathogenesis of polycystic pancreas Reconstruction of cystic elements in one case Am J Path 23 485-499 1947

[5] Norris R F and Tyson R M The pathogenesis of congenital polycystic lung and its correlation with polycystic disease of other epithelial organs Reconstruction of cystic elements in two cases Am J Path 23 1075 1097 1947

development and differentiation of polycystic organs progresses while the cystic lesions are being formed As a consequence of the epithelial cystic proliferation, the ducts or epithelial tubules eventually are pinched off as isolated segments or as dilated cysts This sequence of changes resembles the phenomenon of normal resorption of the provisional organ, the mesonephros In the latter instance, segmentation of tubules and isolation of glomeruli as cysts normally precede the resorption of these elements as the mesonephros degenerates[6] Since the first generations of tubules in the metanephros are also thought to be normally provisional,[7-12] we have suggested that segmentation and cystic dilatation of the tubules in polycystic disease of the kidney and of other organs represent an extension of this normal process of resorption to a pathologic degree In effect the polycystic organ is abnormally provisional[1-5] The evidence presented in the recent paper of Lambert[13] may be interpreted to support this hypothesis In most cases of polycystic disease, however, resorption of a large number of cystic elements apparently does not occur As a consequence, instead of becoming smaller and disappearing, the polycystic organ progressively enlarges as the cysts increase in size Only in a few instances of so-called hypoplastic polycystic disease reviewed by Norris and Herman[14] and in polycystic disease of the pancreas described by Norris and Tyson[4] is there evidence that resorption of tubules and cysts may occur to a significant degree The provisional character of the polycystic organ, therefore, rarely includes the ultimate resorption of the majority of segmented epithelial structures

The epithelial lesions of the hypertrophied prostate characterized by cystic dilatation of ducts and acini and by the isolation of blindly-ending cystic complexes resemble the lesions of congenital polycystic disease Again there is little or no evidence in this disease that a significant number of cysts are resorbed Moore[15] has emphasized, however, that in the case of so-called sclerotic atrophy of the prostate in which proliferation of fibrous tissue is extensive, epithelium and acini may actually disappear Thus in the involution of the otherwise normal glands, proliferation of fibrous stroma and resorption of epithelial elements may

[6] Felix, W The development of the urogenital organs In Keibel, F and Mall, F P (eds ) Manual of Human Embryology Philadelphia J B Lippincott Co , 1912, vol 2, pp 752-979

[7] Kampmeier, O F Über das Schicksal der erstgeformten Harnkanälchen der bleibenden Niere beim Menschen Arch f Anat u Physiol , anat Abteil , pp 204-266, 1919

[8] Kampmeier, O F A hitherto unrecognized mode of origin of congenital renal cysts Surg , Gynec and Obst , 36 208-216, 1923

[9] Kampmeier, O F Weitere Studien über die Entwicklungsgeschichte der bleibenden Niere beim Menschen Ztschr f Anat u Entwcklngsgesch , 73 459-500, 1924

[10] Kampmeier, O F The metanephros or so called permanent kidney in part provisional and vestigial Anat Rec , 33 115-120, 1926

[11] McKenna, C M and Kampmeier, O F A consideration of the development of polycystic kidney Tr Am A Genito-Urin Surg , 26 377-383, 1933

[12] McKenna, C M and Kampmeier, O F A consideration of the development of polycystic kidney J Urol , 32 37-43, 1934

[13] Lambert, P P Polycystic disease of the kidney A review Arch Path , 44 34-58, 1947

[14] Norris, R F and Herman, L The pathogenesis of hypoplastic polycystic kidneys associated with obstruction in the lower urinary tract Report of a case Bull Ayer Clin Lab , Pennsylvania Hosp , 3 407-412, 1941

[15] Moore, R A The evolution and involution of the prostate gland Am J Path , 12 599-624, 1936

progress concurrently It is possible therefore that resorption of acini may also occur in cases of hypertrophy, particularly when found in the aged, such as in cases 2 and 3 of the present report

Hyperplasia of the stroma in hypertrophy of the prostate is a more conspicuous feature than in polycystic disease The fetal connective tissue in association with the polycystic lesions of the newborn is loosely arranged and appears to be no more abundant than the amount of supporting tissue anticipated for epithelial structures of this size and extent Many cases of fibrocystic disease of the pancreas are exceptions to this statement in that the bulk of the pancreas often appears to be preserved by proliferation of fibrous stroma when only remnants of ducts and acini are present If the child survives for a time, the fibrous stroma of the pancreatic lesions may become scarred and hyaline Likewise the stroma about the lesions of congenital cystic disease in the adult, notably in the kidney, is also often scarred, but shows little evidence of active hyperplasia In general, however, proliferation and segmentation of the epithelial structures appear to be the principal lesions in polycystic disease In the case of hypertrophy of the prostate, on the other hand, few agree with Motz and Perearnau[16] and Swyer[17] that adenomatous hyperplasia of the acini is the primary lesion Reischauer [18] [19] Pollak,[20] Deming and Neuman,[21] Le Duc,[22] and Moore[23] [24] support the most widely held view that the initial lesion is hyperplasia of the fibrous and muscular stroma According to this hypothesis, acinar hyperplasia is a secondary manifestation of the disease Regardless of which concept is the correct interpretation, the fact remains that cystic dilatation and segmentation of epithelial structures occur in both diseases

The objection may also be raised that polycystic disease of the newborn differs from hypertrophy of the prostate in the short time required for its development It should be stated, however, that this difference may be more apparent than real if the rapidity of all embryologic development is taken into consideration

So far as the writers know, neither polycystic disease nor hypertrophy of the prostate have been reproduced experimentally in animals The cause of each disease, therefore is obscure Whether there are etiological factors in common is still unknown but the possibility should not be ignored In the case of hypertrophy of the prostate, the belief persists that imbalance of endocrine secretions is the cause of the disease The evidence in favor of this hypothesis may be found in the reviews of Hirsch,[25] Pollak,[20] MacCallum,[26] Moore,[24] Huggins and Webster,[27] Richter,[28] and Reischauer [29] Endocrine disturbances during pregnancy, however, have not been extensively investigated as a cause of polycystic disease

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[16] Motz B and Perearnau Contribution a l étude de l évolution de l hypertrophie de la prostate Ann d mal des org genito urin 23 1521-1548, 1905

[17] Swyer G I M Some observations on the pathological anatomy of benign prostatic enlargement J Path and Bact 56 365-375 1944

[18] Reischauer F Die Entstehung der sogenannten Prostatohypertrophie Virchows Arch f path Anat 256: 356-389, 1925

[19] Reischauer F Über die formale Genese der sogenannten Prostatohypertrophie Bruns Beitr z klin Chir 160 460-483 1934

[20] Pollak W Zur Genese der Prostatohypertrophie Ztschr f Urol 31 47-67, 1937

[21] Deming C L and Neuman C Early phases of prostatic hyperplasia Surg Gynec & Obst 68 155-160 1939

[22] Le Duc, I E The anatomy of the prostate and the pathology of early benign hypertrophy J Urol 42 1217-1241 1939

[23] Moore R A Benign hypertrophy of the prostate A morphological study J Urol 50 680-710 1943

[24] Moore R A Benign hypertrophy and carcinoma of the prostate Occurrence and experimental production in animals Surgery 16 152-167 1944

From the foregoing discussion, the conclusion seems warranted that the similarity of the lesions of hypertrophy of the prostate and of congenital polycystic disease are important not only because lesions of embryologic development can be mimicked in the organs of adults, but also because the two diseases may have etiologic factors in common

## SUMMARY

The similarity of the lesions of hypertrophy of the prostate and of polycystic disease of the newborn is described, and the lesions in the prostate are illustrated by means of reconstructions from serial sections in three cases The significance of this similarity is discussed

The authors wish to thank Mrs James Butcher for preparing the drawings of the reconstructions, Miss Dorothy J Loeb for preparing the serial sections, and Mr R L Chapman for the photomicrographs

[25] Hirsch, E F Pathology of prostatic hypertrophy J Urol , **35** 227-234, 1936

[26] MacCallum, W G Pathologic physiology of the prostate Physiol Rev , **17** 73-91, 1937

[27] Huggins, C and Webster, W O Duality of human prostate in response to estrogens J Urol , **59** 258-266, 1948

[28] Richter, W H Morphologisch experimentelle Untersuchungen zum Problem der Prostatohypertrophie, morphologisch-experimenteller Teil Ztschr f Urol , **43** 185-208, 1950

[29] Reischauer, F Über die formale und kausale Genese von Prostatohypertrophie und Prostatkarzinom Ztschr f Urol , **43** 353-375, 1950

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# CARCINOMA OF THE PROSTATE: FIVE-YEAR FOLLOWUP OF PATIENTS TREATED BY RADICAL SURGERY

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The difference between curable cancer and incurable cancer is simply the difference between detection and adequate treatment "on time" and detection and treatment "too late."

Early detection is essential for cure by radical surgery. This detection can be made only by periodic examination of men past 40. When clinical symptoms occur the disease process is too far advanced for cure by any form of treatment.

The incidence of cancer of the prostate has increased during the past two decades. In 1935[1] Rich reported an incidence of 14 per cent in 292 consecutive autopsies in patients over 50, Baker,[2] 1953, reported an incidence of 24 per cent. Since carcinoma of the prostate is chiefly a disease of men past 50, the increase is due in a great measure to the fact that more men are living longer.[3]

TABLE 1. *Age group per population*[3]

| Year | Population | Age Over 45 Yrs. | Age Over 65 Yrs. |
|---|---|---|---|
| | *millions* | *per cent* | *per cent* |
| 1850 | 23.0 | 12.4 | 2.0 |
| 1900 | 76.0 | 17.8 | 4.1 |
| 1950 | 152.0 | 28.4 | 8.2 |
| 2000* | 200.0 | 41.0 | 14.0 |

* Forecast.

TABLE 2. *Incidence of carcinoma of prostate by age group*[4]

| Age | Per Cent |
|---|---|
| 40–49 | 4 |
| 50–59 | 5 |
| 60–69 | 18 |
| 70–79 | 32 |
| 80–90 | 48 |
| Over 90 | 83 |
| Total over 80 | 53.8 |

The population of these United States has more than doubled since 1900. A part of this growth can be attributed to the increased longevity rather than to the addition of new young stock. The internal structure of the population is shifting toward an increasingly greater proportion of older people.

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Read at annual meeting, Mid Atlantic Section of American Urological Association, Hot Springs, Va., April 20, 1956.

[1] Rich, Arnold Rice: Occult carcinoma. J. Urol., 33: 215–219, 1935.

[2] Baker, Roger: Studies in cancer prevention. Ann. Surg., 137: 29–34, 1953.

[3] Volz, C. J.: Manpower prospects. J. A. M. A., 147: 1319–1320, 1951.

[4] Hirst, A. F. and Bergman, T. R.: Cancer, 7: 136–141, 1954.

TABLE 3 *Prostatism among[5] urologic admissions to Howard University*

| Urologic Admissions 1945-1954 | Cases of Prostatism | Benign | Malignant |
|---|---|---|---|
| 2856 | 805—28% | 603—21% | 202—7% |

Ca prostate 1 in every 14 urologic admissions
*Ca prostate 1 in every 4 cases of prostatism*

TABLE 4

| BPH | Carcinoma | Total | % Ca |
|---|---|---|---|
| 801 | 164 | 965 | 17 |

Life expectancy in 1900 was little more than 45 years At present time this expectancy is more than 65 years In 1900, 4 1 per cent of the population was over 65 and 8 2 per cent in 1950 The estimated percentage of this group is 14 per cent in 2000 A D is shown in table 1

Table 2 shows the increased incidence occurring as the age of the individual became greater

Jones[5] found an incidence of carcinoma of the prostate of 1 in every 14 urological hospital admissions and 1 in every 4 cases of prostatism (table 3)

At Walter Reed Army Hospital, during the period 1940–1953, there were 164 (17 per cent) carcinoma cases in 965 patients treated for prostatism (table 4)

A review of these data emphasizes the increasing number of individuals each year with cancer of the prostate and the importance of early detection and radical surgical treatment

American medicine has adequate organization for early detection of cancer of the prostate There have been numerous publications in the popular lay press concerning the importance of early diagnosis, chiefly of the female breast and cervix Rarely has mention been made of the importance of periodic examination of the prostate and male genitalia Cancer of the prostate is readily detected early in 80–90 per cent of cases

In the cancer detection clinics of the Washington, D C, vicinity, less than 20 per cent of those reporting for examination are men[6] This simply indicates that the male has not become "cancer minded" and is neglecting the periodic examination of the prostate before it is too late for surgical cure

Digital rectal examination is the only clinical procedure by which early detection can be made A nodular or hard prostate or fixed prostate demands further investigation The rectal examination has been more than 90 per cent accurate in the Urology Service, Walter Reed Army Hospital The digital rectal examination and open perineal biopsy when indicated have given the correct early diagnosis in almost all cases

When clinical symptoms are present only 5 per cent are amenable to surgical cure More than 80 per cent have origin in the posterior lamella and would

[5] Jones, R F J Nat Med Assn, 47 147–157, 1955
[6] Personal communication, Tumor Registry, AFIP

TABLE 5 *Methods of diagnosis*[7]

- Digital rectal examination
- Digital rectal examination and perineal open biopsy
- Transurethral resection
- Perineal needle biopsy
- Cytology
- Ketosteroids
- Enzymes
    - Acid phosphatase
    - Alkaline phosphatase
    - Chymotrypsin
    - Rennin

probably not be detected early by transurethral resection Perineal needle biopsy has been accurate in late cases, in which it is not necessary, and often gives a misleading negative result in the early stages of the disease

Acid phosphatase, alkaline phosphatase, rennin, and chymotrypsin determinations and positive x ray findings are indicative of late manifestations Androgen determination has not been helpful Cystoscopy is of little value in early cases Cytological examination has doubtful value, its chief benefit is due to the fact that a digital rectal examination is necessary to obtain the specimen for study

Estrogen therapy will reduce the size of the nodules and lessen the hardness in 80 per cent of cases

## TREATMENT

Radical surgical extirpation is indicated in the following types of patients

1) The malignant process has not extended beyond the capsule of the prostate or seminal vesicles or encroaches upon the region of the membranous urethra as demonstrated by rectal palpation The gland must be freely movable fixation indicates extension beyond the capsule

2) The absence of evidence of metastases

3) *A good surgical risk with life expectancy of more than 2 years* Age *alone* does not contraindicate radical surgery if the patient is in good physical condition The youngest in the series of 56 radical operations was 43, next youngest, 51, the oldest 82 and the average age was 64

Borderline cases (in which the local extension is doubtful) are given preoperative estrogen therapy prior to radical surgery These cases are treated by radical surgery because the mortality is minimal and the problem of subsequent urinary retention is eliminated

In case the pathological examination of the tissue removed indicates extension beyond the excised parts, castration and hormone therapy are begun without delay Eight patients have been treated in this manner, 5 of these are living and well at 5 years, 2 are dead of carcinoma, and 1 of coronary disease

Gold isotope injection into the prostate and periprostatic tissue as a curative treatment for patients with local extension has been used with favorable results in some urological clinics It has not been used at Walter Reed Army Hospital

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[7] Colby F H Carcinoma of the prostate J Urol 69 797-806 1953

TABLE 6 *Three year survival in carcinoma of the prostate*

| | Cases | 3 yr Survival |
|---|---|---|
| | | % |
| Control (Nesbit and Plumb) | 273 | 22 |
| Stilbestrol (Nesbit and Baum) | 143 | 49 7 |
| Castration (Nesbit and Baum) | 239 | 53 4 |
| Castration and stilbestrol (Nesbit and Baum) | 159 | 66 |
| Endocrine therapy plus radical prostatectomy (Scott) | 21 | 85 7 |

Palliative treatment is given to patients in which the disease is too widespread to be cured by radical surgery and those in which the pathological report indicates that the malignancy was not completely removed by the operative procedure Palliative therapy is initiated without delay in these patients This treatment consists of castration and estrogen therapy in dosage of 5–50 mg daily as tolerated TACE has given good results in some patients, but has not been used to an extent and duration to justify proper evaluation

When the beneficial effects of castration and estrogen therapy become ineffective and no longer give relief, androgen, teropterin and other "fringe cancer remedies" are given a trial Transurethal resection and cystostomy are occasionally indicated Pain in terminal cases may be relieved by irradiation, prefrontal lobotomy, and chordotomy Adrenalectomy has been done in three patients to relieve pain when other measures failed

Postoperative followup, x-ray and serum acid phosphate determination are carried out at 3-month intervals during the first and second years and annually after the second year

Colston and Brendler[8] have reported patients in whom the initial rectal examination indicated extension beyond the capsule who were rendered available for radical surgery by preoperative estrogen therapy and/or castration The cure in these patients is questionable, certainly life has been prolonged and the distress ameliorated

Winfield W Scott[9] reported a series of 21 cases treated by radical surgery 4 months to 4 years following estrogen therapy and castration The 3-year comparative survival rate shown in table 6 demonstrates the value of this procedure

*Technique of the operation* The perineal approach was used in all but 1 case in which the retropubic procedure was done The gland and seminal vesicles were usually removed in one piece with as little manipulation as possible The anterior layer of the fascia of Denonvilliers was removed The seminal vesicles and the surrounding fascia were extirpated The ureteral orifices were visualized and catheterized if ureteral damage was imminent The anastomosis of the bladder neck to the urethra and triangular ligament was made watertight After the operation the thighs were wrapped and lowered slowly

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[8] Colston, J A C and Brendler, H Endocrine therapy in carcinoma of prostate J A M A , **134** 848, 1947

[9] Scott, W W Endocrine control of carcinoma of prostate Cancer, **6** 248–265, 1953

The posterior layer of Denonvilliers' fascia was left intact to avoid rectal injury. This practice is debatable. Its removal leaves the rectum thin and bare but might decrease the rate of recurrence.

### PROGNOSIS

During the 11 year period 1940–1950, 100 patients were treated for carcinoma of the prostate. A 5 year followup has been carried out and the survival rate ascertained. Fifty six (56 per cent) were treated by radical operation, 44 (44 per cent) were too far advanced for radical surgery and were treated by palliative measures.

Table 7 shows the 5-year survival rate.

TABLE 7. *Carcinoma of prostate. Five year survival rate, Walter Reed Army Hospital 1940–1950*

| Total Patients | | | Living | | | Dead | | | Unknown | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pal. | Rad. | Total | Pal. | Rad. | Total | Pal | Rad | Total | Pal | Rad | Total |
| 44<br>44% | 56<br>56% | 100 | 11<br>25% | 36<br>64.3% | 47<br>47% | 31<br>70.5% | 15<br>26.8% | 46<br>46% | 2<br>4.5% | 5<br>8.9% | 7<br>7% |

Thirty-six patients (64.3 per cent) treated by radical surgery are living and well at the end of 5 years. Eleven (25 per cent) treated by palliative measures survived 5 years. This 5 year survival rate compares favorably or parallels the 5 year survival rate reported by Colby,[7] Jewett,[10] and others. It establishes definitely the great advantage of early diagnosis and radical surgery.

Fifteen patients who underwent radical surgery are known to be dead, *four* died of cancer and *eleven* died of other causes. Almost all the 31 deaths in the palliative group were due to cancer.

One hospital death followed radical surgery. A patient 80 years of age, after uneventful recovery, died of pulmonary embolism on the thirteenth postoperative day.

### CONCLUSIONS

Digital rectal examination should be done annually in all men over 40 years of age.

The nodular hard or fixed prostate should have open surgical biopsy.

Following early diagnosis, radical surgery is the treatment of choice.

Annual digital rectal examination of men over 40 followed by adequate biopsy and radical surgery offers the only hope of reducing the mortality and morbidity of prostatic carcinoma.

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[10] Jewett, H. J. Radical perineal prostatectomy for carcinoma. J. A. M. A. 156 1039–1041, 1954.

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# RAPID SPECIATION OF THE GENUS PROTEUS

ROBERT E HOYT, MIRIAM SELTZER AND M J PICKETT

*From Division of Laboratories, Cedars of Lebanon Hospital and Department of Bacteriology, University of California, Los Angeles, Calif*

Members of the genus Proteus have become the object of increasing interest in recent years, mainly because of their resistance to antibiotic drugs and their apparently increasing presence in infections Potee, Wright and Finland studied the *in vitro* response of recently isolated strains of Proteus to antibiotics, and found certain variations with respect to species, *P mirabilis* generally being more susceptible than the other members of the group when tested against penicillin, chloramphenicol and streptomycin P vulgaris strains were susceptible to tetracycline analogues, whereas P morganii and P rettgeri were of varying sensitivity and P mirabilis strains were moderately to highly resistant

The importance of Proteus strains in urinary infections is well known, and considerable evidence links Proteus to intestinal disorders, particularly enterocolitis in infants The observations of Potee et al suggest that speciation may have more than a taxonomic value, and may furnish a guide to empirical antibiotic therapy in cases where it may not be practical to carry out *in vitro* sensitivity studies With this in mind we have investigated the speciation of the genus Proteus with the aim of providing a scheme which can be followed in an office laboratory and making use of rapid procedures similar to those described for the identification of the enteric organisms (Pickett, Scott and Hoyt)

*Bergey's Manual of Determinative Bacteriology* divides the genus into four species which are separated on the basis of carbohydrate fermentations and on indole formation However, Proteus is a proteolytic and ammonifying organism whose fermentative abilities are somewhat limited and variable, thus, such qualifying terms as "(delayed)", "(ordinarily)" and "occasionally" appear in the key to the genera Obviously reactions which are likely to be delayed are not suited to rapid identification, so we have selected certain others for study which are brought about more promptly by those strains which are positive These include the indole and Voges-Proskauer tests, $H_2S$ production, gelatin liquefaction and the formation of acid from mannitol (The latter reaction was included because it is needed to distinguish P morganii and P rettgeri, and is more prompt than the fermentation of sucrose ) In addition to these tests, reactions on sucrose and mannitol were recorded so that the strains could be identified according to the Bergey scheme

## PROCEDURE

Strains of organisms presumed to be members of the genus Proteus were isolated in the course of routine study of stool and urine specimens Colonies which showed no fermentation of lactose on differential media were transferred to slants of Kligler's iron agar medium Those organisms which fermented dex-

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trose but not lactose were tested for urease production using tablets similar to *those described by us but modified to conform to the formula of Christensen* Since the urea substrate is weakly buffered, the reaction catalyzed by urease is rapid and in most cases can be read in 2–3 hours Cultures which are positive at this time usually turn out to be Proteus strains, although an occasional para colon organism is able to bring about rapid hydrolysis of urea Organisms which were lactose negative and urease positive were tested for their ability to ferment sucrose, maltose and mannitol using the tablet substrates described by Pickett, Scott and Hoyt The Voges Proskauer test was performed using the pyruvate tablet described by Pickett and indole formation was tested using the tryptophane substrate tablet Gelatin liquefaction was demonstrated by immersing strips of photographic film in a suspension of the organism being tested Liquefaction was shown by the clearing of the film base as the digested gelatin slips off

The use of tablet substrates* will be described in detail elsewhere in connection with studies on paracolon and related micro-organisms In brief, each tablet contains the ingredients necessary to study a single reaction, a tablet is dissolved in 1 ml distilled water and seeded with 2–3 drops of a heavy inoculum In this small volume the reaction takes place rapidly and is not disturbed by the presence of an occasional contaminant The indole and Voges Proskauer reactions are read at 4 hours, Kovak's reagent is used to develop the color in the indole test, and solutions of alpha naphthol and KOH are used in the Voges Proskauer reaction as described by Barritt The gelatin and fermentation tubes were read *at intervals up to 48 hours, in practically all cases fermentation could be detected* in 4–8 hours Gelatin liquefaction is usually rapid being observed in 2–4 hours, but negative tests were held 18–24 hours before discarding $H_2S$ formation was observed in the Kligler iron agar tube All incubations were at 37°C

It has been shown that in carrying out the rapid determinations the size of the inoculum is very important We have found that a satisfactory inoculum is prepared by suspending the growth from the Kligler slant (or any agar slant giving comparable growth) in 1–1 5 ml distilled water The surface of the slant should be approximately 20 mm long to give a suspension of sufficient density

## RESULTS

*It became apparent at once that certain reactions usually appeared in com*bination Thus, those strains which were $H_2S$ producers in most cases liquefied gelatin, while strains which did not liquefy gelatin never produced $H_2S$ However, 6 strains which were $H_2S$ negative were gelatin positive these were culturally identified as P mirabilis since all were Voges Proskauer positive and all but one fermented sucrose Inasmuch as $H_2S$ production is apparent from inspection of the Kligler slant and gelatin liquefaction can be determined rapidly, we considered these features as points for preliminary separation As gelatin liquefaction appeared to be slightly more sensitive, it was chosen to be used

Those strains which were gelatin liquefiers could be separated into two distinct

---

* Substrate tablets were obtained from Key Scientific Products Company P O Box 66514 Los Angeles Calif

TABLE 1 *Speciation of 104 strains of Proteus*

| Reactions | No Strains | | Designation |
|---|---|---|---|
| I Gelatin liquefied<br>A Indole +<br>Voges-Proskauer −<br>Maltose +<br>Mannitol −<br>Sucrose + | 78 | 11 | P vulgaris |
| B Indole −<br>Voges-Proskauer +<br>Maltose −<br>Mannitol −<br>(Sucrose + 61) | | 67 | P mirabilis |
| II Gelatin not liquefied<br>A Indole +<br>Mannitol +<br>(Sucrose + 4) | 26 | 5 | P rettgeri |
| B Indole +<br>Mannitol −<br>(Sucrose + 2) | | 21 | P morganii |

TABLE 2 *Proposed key to the speciation of the genus Proteus*

| | |
|---|---|
| I Gelatin liquefied, $H_2S$ usually produced | |
| A Indole formed, acetyl methyl-carbinol not formed | P vulgaris |
| B Indole not formed, acetyl-methyl-carbinol formed | P mirabilis |
| II Gelatin not liquefied, $H_2S$ not produced | |
| A Indole formed | |
| 1 Mannitol fermented | P rettgeri |
| 2 Mannitol not fermented | P morganii |

groups on the basis of the Voges-Proskauer and indole tests Of 78 strains tested, 67 were Voges-Proskauer positive and indole negative, while 11 gave the reciprocal pattern The 11 strains gave the characteristic reactions of P vulgaris, fermenting maltose but not mannitol or sucrose The 67 strains were identified as P mirabilis, none fermented maltose or mannitol, and 61 fermented sucrose Thus it appears that the three points of gelatin liquefaction, indole formation and the Voges-Proskauer reaction can distinguish P vulgaris and P mirabilis from each other and from the other members of the genus

All those strains which were unable to liquefy gelatin were indole positive and were found to be either P rettgeri or P morganii Separation was based upon the ability to ferment mannitol, 5 strains fermented mannitol, 4 of which also fermented sucrose, and were considered to be P rettgeri Sixteen strains were unable to ferment mannitol, and of these 2 were able to ferment sucrose This group was classed as P morganii The results are shown in table 1, and the suggested key is outlined in table 2

## DISCUSSION

The key as presented here has several points to recommend it In the first place, it depends upon reactions which are uniform rather than the more variable sugar fermentations Second, the number of tests actually required to speciate the strains is reduced to four, gelatin liquefaction, formation of indole and acetyl-methyl-carbinol (Voges Proskauer reaction) and the fermentation of mannitol These tests are convenient to perform using the tablet substrates, and the reactions take place rapidly The fermentation of mannitol is the only one which may be delayed while the other reactions are read after 4 hours (the liquefaction of gelatin is almost invariably apparent at this time) It is worth observing that in case $H_2S$ is produced on the Kligler slant it is not necessary to inoculate mannitol, since speciation is accomplished on the basis of the indole and Voges-Proskauer reactions with these organisms

The possible value of such information relating to antibiotic therapy has been suggested in the opening section Another benefit to be derived from the practice of complete identification lies in the higher level of bacteriological performance which it promotes It is our feeling that a bacteriologist should attempt to name organisms isolated whenever possible Good professional standards seem to demand that such an effort be made, and furthermore, the analysis of published material will become much more valuable when bacteriological identifications are as complete as possible

## SUMMARY

A key to the systematic speciation of the genus Proteus is described, based on the four species recognized in Bergey's Manual Identifications are made on the basis of tests for indole, acetyl methyl carbinol (the Voges Proskauer reaction), gelatin liquefaction and fermentation of mannitol using the rapid substrate technique The procedures give results which compare well with the Bergey key and are much faster, in most cases identification of species can be made after 4 hours' incubation All can be performed conveniently in the office laboratory

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Iotee K C Wright S S and Finland M In vitro susceptibility of recently isolated strains of Proteus to ten antibiotics J Lab & Clin Med 44 403–477 1954

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# AIR CYSTOMANOMETER

HOSSEIN GOLJI*

*From the Department of Urology, Wayne University College of Medicine, Detroit 26, Mich*

Cystometrogram study in urological patients is an almost routine procedure for a complete and satisfactory workup Diagnosis and understanding of the bladder detrusor contractility and adaptability are two of the prerequisites required for adequate treatment of any prostatic or obstructing lesion of the lower urinary tract In spinal cord and brain injuries, tumors, and in specific or nonspecific infections of this system, cystometrogram study is of great value It helps in the understanding of the various neurological disturbances of the bladder and in the proper management of patients Also, a routine cystometrogram study in many instances has been the key in detection of neurological diseases which would not have been suspected otherwise

To accomplish the aforementioned purposes a few models of cystometer are available such as Rose's revolving drum, Lowsley's mechanical pressure gauge, Munro's water manometer, Landes electrocystometrograph, Milam and Leberman recording cystometer, electrocystometer of Lloyd Lewis and mercury cystometer of Muschat All these devices are accurate and well designed particularly the last two, whereas for routine use and examinations they are heavy, difficult to handle, expensive and necessitate extra equipment

It is the purpose of this paper to present another model of cystometer which I call the air cystomanometer This apparatus is similar to a blood pressure device and is very easy to carry around and to use everywhere It is composed of the following pieces of equipment (fig 1) a) one manometer showing 0 to 160 mm of mercury pressure, b) a 50 cc syringe, c) four pieces of No 18 rubber tubes and d) three 3-way stopcocks All parts of the apparatus are removable and therefore they may be readily sterilized after each use

After connection of the device with an indwelling Foley catheter, directions for the operation of the air cystomanometer are as follows (fig 2)

1) Set the manometer to zero by connecting the bladder with gauge through the stopcocks 2 and 3 and moving the gauge to the level of the bladder Also, draw the desired amount of air into the syringe through the stopcock 1 (fig 2, a, first step)

2) Set the stopcocks 1 and 2 in such a position that the air may be injected into the bladder (fig 2, b, second step)

3) Adjust stopcocks 2 and 3 in such a position that intravesical pressure may be read on the manometer (fig 2, c, third step) After reading intravesical pressure the manometer may be set back to zero by connecting the gauge with atmosphere through stopcock 3

4) Repeat the above procedures for second, third and fourth times and so on until the maximum capacity of the bladder is reached

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* Present address Urology Department, The Grace Hospital, Detroit, Mich

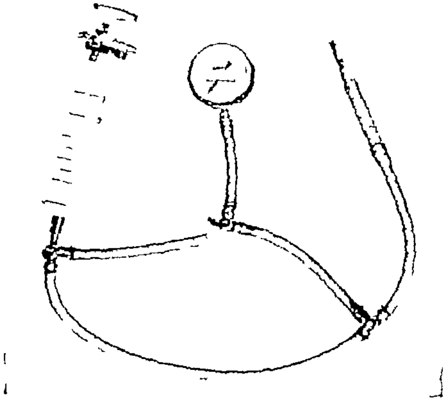

Fig 1

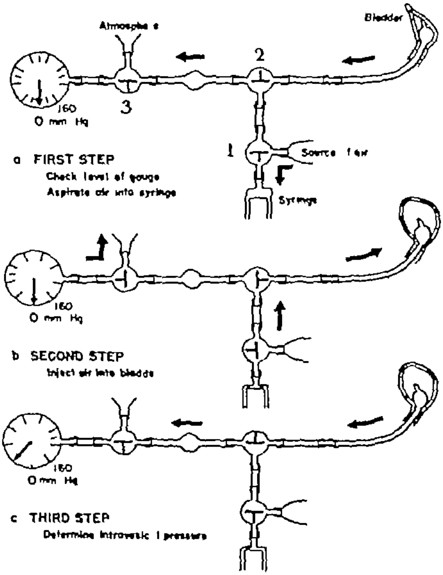
Atmosphe e
Bladder
2
3
160
0 mm Hg
1
Source f air
Syringe
a FIRST STEP
Check level of gauge
Aspirate air into syringe
160
0 mm Hg
b SECOND STEP
Inject air into bladde
160
0 mm Hg
c THIRD STEP
Determine intravesic l pressure

Fig 2

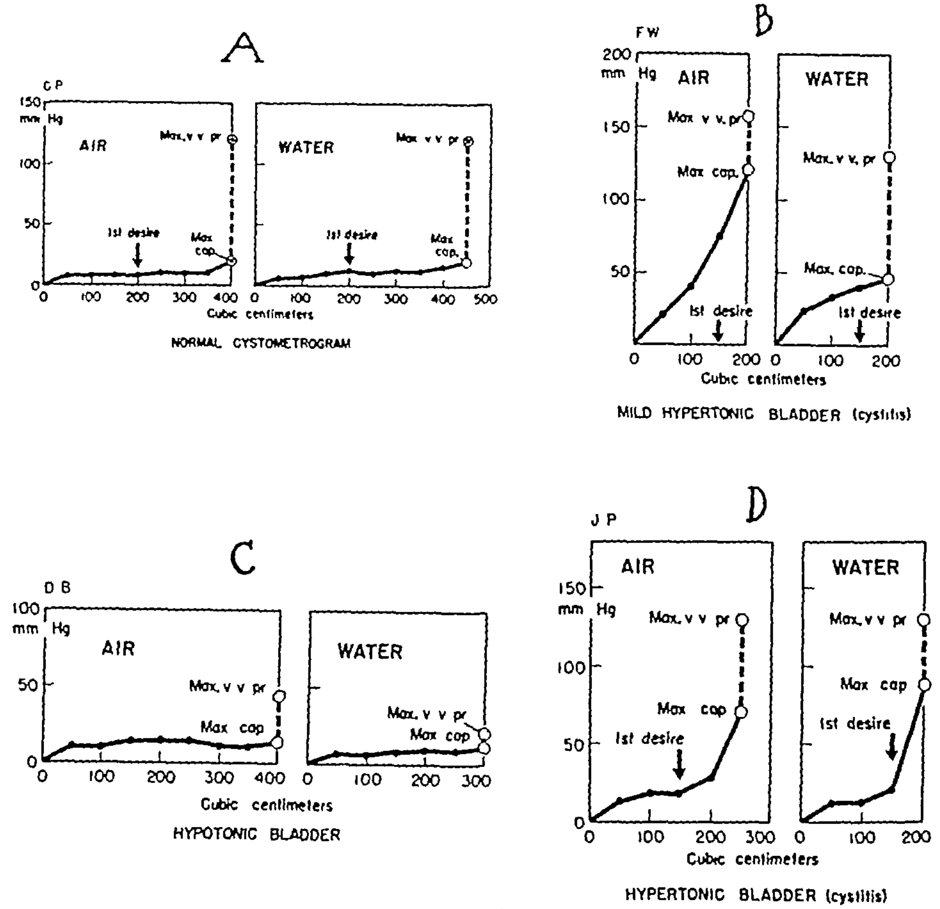

Fig 3

The rubber bulb between stopcocks 2 and 3 prevents any leakage of drops of urine into the gauge

To get satisfactory and uniform results a) use intact tubes and connect the different parts of apparatus hermetically to prevent the leakage of air b) Put the patient in a supine and flat position to prevent changes from the extra pressure exerted by abdominal contents c) Use a No 18 Foley catheter with a 5 cc bag for catheter retention Keep slight tension on it

Interpretation of the results of the examination lie in the understanding of

a) Contractility of the bladder detrusor (stretch reflex) This is the first rise of the handle right after connecting the bladder with the manometer when the air is injected

b) Adaptability of the bladder detrusor which is recorded when the handle of manometer stays fixed within 1–2 minutes after connecting the bladder with the gauge

c) Instability of the bladder detrusor contractility (fibrillation of the bladder)

d) Maximum voluntary pressure for voiding (maximum intravesical pressure)

e) Capacity of the bladder, desire of urination, and the subjective sensory changes

## CONCLUSIONS

The use of the air cystomanometer has proved to be comparable to the other types of complicated devices in regard to accuracy

The air cystomanometer is much less cumbersome and may be used everywhere

This device is inexpensive and simple

One may quickly learn to handle this apparatus and the principle by which it works

No complications or morbidity have been noticed during or after the use of this device in a series of over 100 cases

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# A SELF-SEALING MODIFICATION OF THE FOLEY CATHETER

JOHN A HUTCH

One of the most awkward maneuvres in common usage by urologists is the filling and emptying of the balloon of the Foley catheter The insertion of a small glass ball into the lumen of the rubber tube through which the balloon is filled greatly simplifies this procedure The glass ball is advanced up the lumen of the inlet tube to a point at which the diameter of the ball is greater than the diameter of the lumen of the tube At this point the elasticity of the rubber tube grips the ball tightly and seals the tube To open the valve pressure is applied on the inlet tube over the glass ball See figure 1, *A* and *B*

To fill the balloon of a catheter so equipped is accomplished by inserting the tip of a syringe filled with water into the open end of the inlet tube leading to the balloon This is operated with the right hand Pressure over the glass ball exerted by the thumb and index finger of the left hand opens the valve, then the contents of the syringe are emptied, filling the balloon The pressure exerted by the left hand is then released, closing the valve To release the contents of the balloon, pressure is exerted over the glass ball, opening the valve

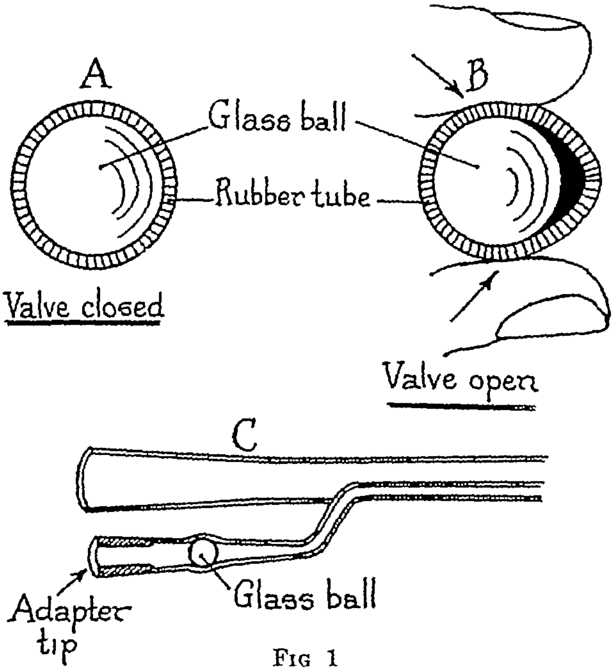

Fig 1

A second feature has been the redesigning of the inlet tube to accomplish two purposes 1) to prevent inadvertent escape of the glass ball, 2) to allow any standard syringe to fit the end of the inlet tube snugly Figure 1, *C* is a sagittal section of the redesigned inlet tube with the glass ball in place

The catheter has been in use for 18 months and has performed quite satisfactorily during that time

I wish to thank Mr E S Outwin and C R Bard, Inc for their help in designing this catheter

*2100 Monument Blvd , Pleasant Hill, Calif*

Accepted for publication March 22, 1956

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*Mid Atlantic*—Cavalier Hotel Virginia Beach Va. March 21-24 1957
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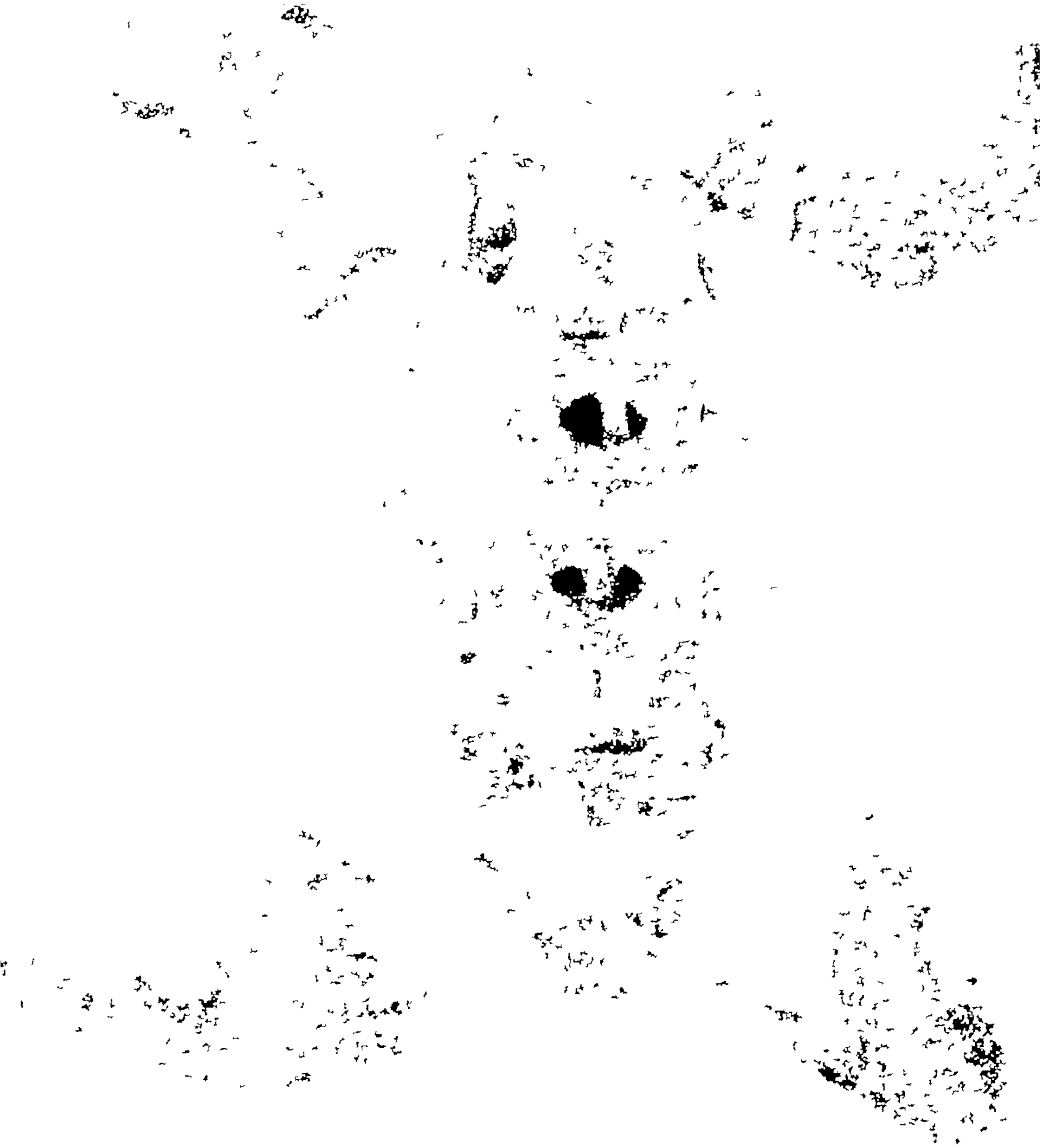
*North Central*—Cleveland, Ohio October 3-5 1956
*South Central*—Mexico City, Hotel Del Prado October 28-31 November 1 1956
*Southeastern*—Atlanta, Ga. April 7-11, 1957

*Note by editor* A complete list of the executive committees of the various sections, and a complete list of the officers and members of the executive committees of the various branch societies will be printed in the December 1956 issue



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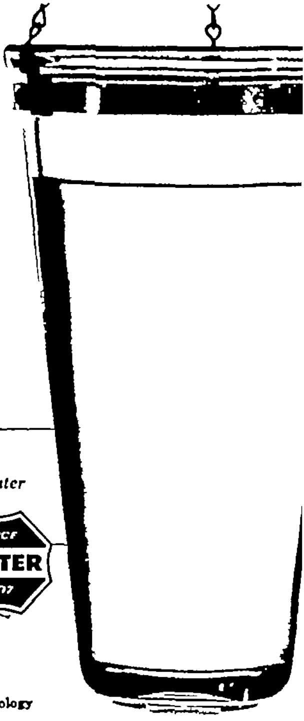

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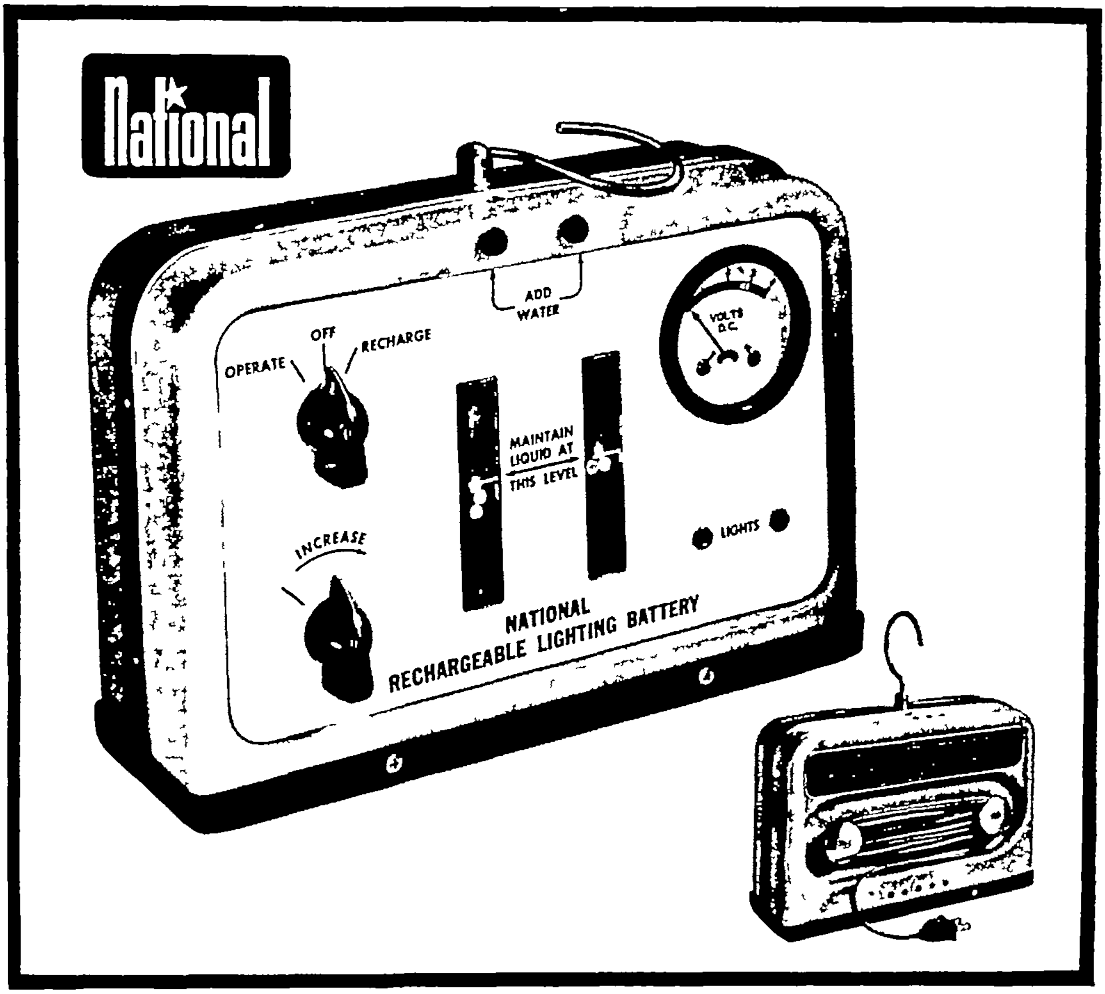
2. T L. Schulte H. J Hammer & L. R. Reynolds Clinical use of Cytal in Urology The Journ. of Urol., Vol. 71 5 May 1954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*Dr V H Wallingford of Mallinckrodt Chemical Works synthesized this compound known as Urokon Sodium Brand of Sodium Acetrizoate in 1945

1 Nesbit Reed Editorial Radiology and Its Contribution to Urology The American Journal of Roentgenology 75 995 (May 1956)

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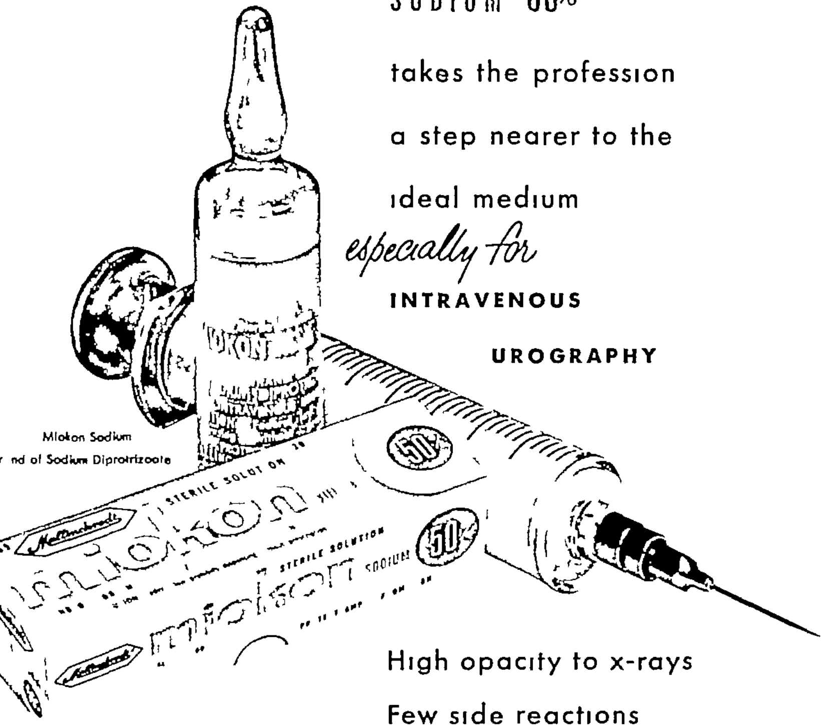
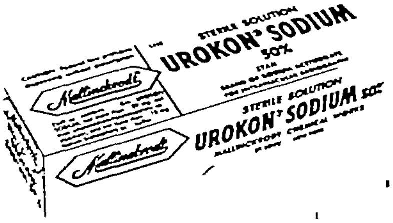


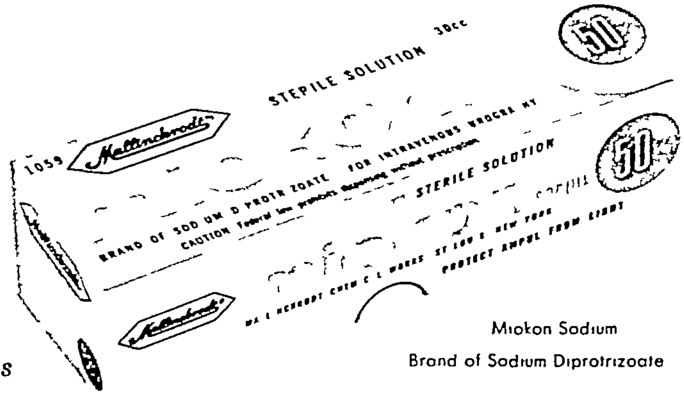
High opacity to x-rays

Few side reactions

Notably safe

MIOKON was perfected in the laboratory several years ago clinically tested under controlled conditions and used routinely in the field for over a year before its general introduction last December





Miokon Sodium
Brand of Sodium Diprotrizoate

**AND NOW**

*Mallinckrodt highly recommends*

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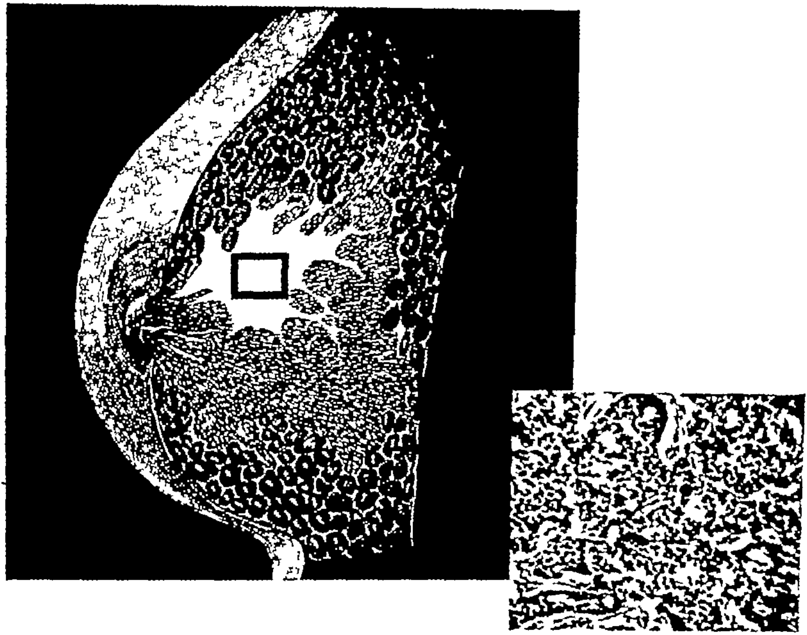
IN CANADA **MALLINCKRODT CHEMICAL WORKS LIMITED** 378 ST PAUL STREET W MONTREAL

# in **breast carcinoma . . .** palliation smoothly maintained with Perandren® phenylacetate



Androgens – in large doses – can provide palliation in advanced inoperable mammary cancer *Of all clinically used* androgens, Perandren phenylacetate provides longer and stronger anabolic and androgenic effects – which are easily obtained, smoothly maintained.

*One dose is usually effective for a full month*

The virtually painless injection of Perandren phenylacetate spares the cancer patient much discomfort, frequency of injections, inconvenience.

Treatment should be started with short acting Perandren *propionate* – *150 to 300 mg weekly* When optimal dosage has been determined the same amount of Perandren *phenylacetate* can then be injected – *once a month.*

Perandren® phenylacetate (testosterone phenylacetate CIBA) Multiple-dose Vials, 10 ml each ml containing 50 mg Perandren phenylacetate Perandren® propionate (testosterone propionate U S P CIBA) Ampuls 1 ml., each containing 25 mg Perandren propionate, Multiple-dose Vials, 10 ml., each ml. containing 25, 50 or 100 mg Perandren propionate

**C I B A**
SUMMIT N J

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When interstitial radiation is indicated, the ALL GOLD radon implant is recommended.

Our radon implants are ALL GOLD—24 Karat—and excellent for intratumoral implantation.

High temperature sterilization is possible with utmost safety.

Accurate dosage is assured because the ALL GOLD radon implant is sold with a guarantee as to radon content at hour of use.

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AMBUTAINER TYPE G DRAIN CAPS fit all the NEW TYPE CUTTER LABORATORIES intravenous bottles-and 1-gallon bottles-for use as drainage receptacles.

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TYPE A for Abbott
TYPE B for Baxter
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Mac Bick Fenwal
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***For the patient, “The treatment is shorter and more comfortable than with the conventional method”****

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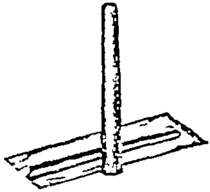
- *proved*—“The suppository method of medication has proved its worth.”* in bacterial (granular) urethritis for prophylaxis and pain relief before and after instrumentation

***to prevent cross infection***

**FURACIN®** vaginal Suppositories are used with Furacin Urethral Suppositories to prevent cross infection from the vagina. Hermetically sealed in yellow foil. Box of 12.

*Youngblood V. H. J. Urol. 70 926, 1953



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BRAND OF NITROFURAZONE
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*Each Furacin Urethral Suppository contains 0.2% Furacin (brand of nitrofurazone) and 2% diperodon HCl in a water miscible base. Hermetically sealed in silver foil. Box of 12*

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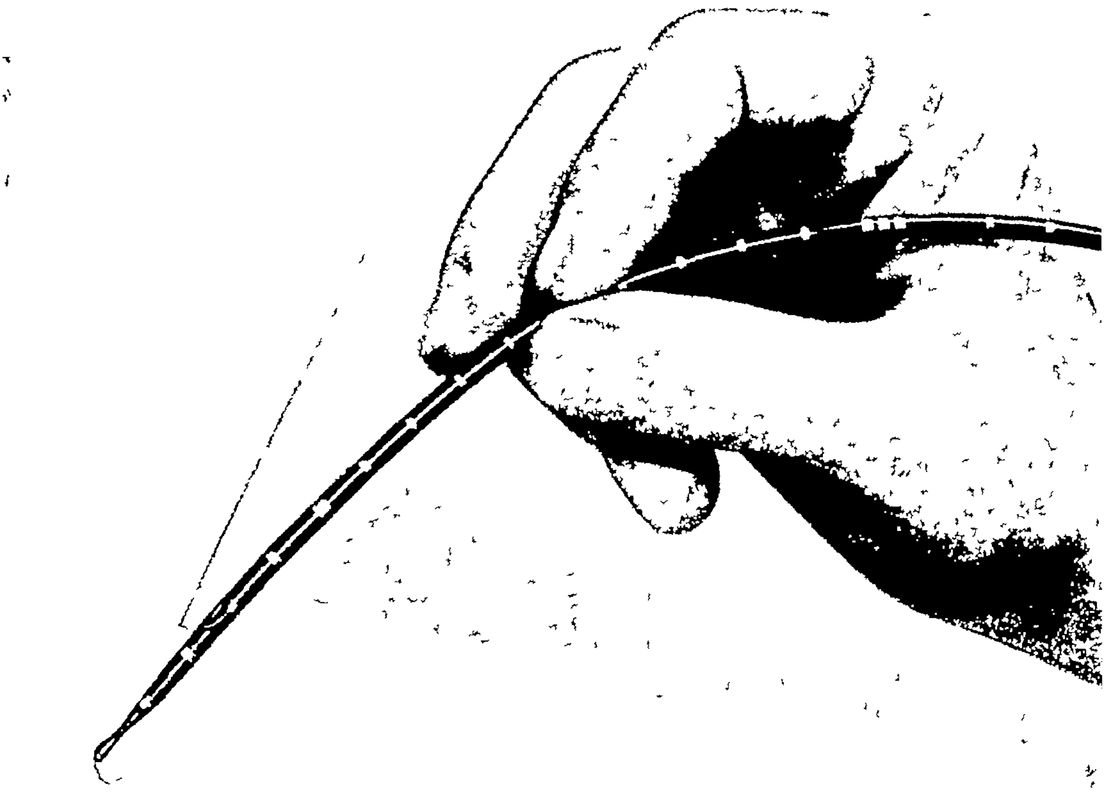

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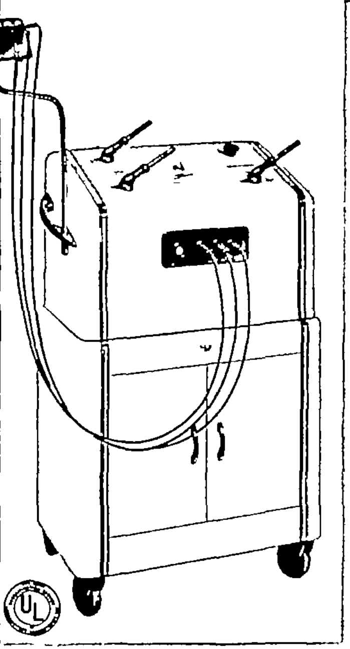

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**ELECTROSURGICAL UNIT**
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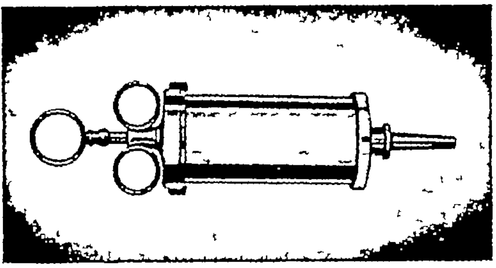

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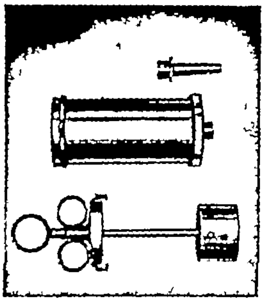

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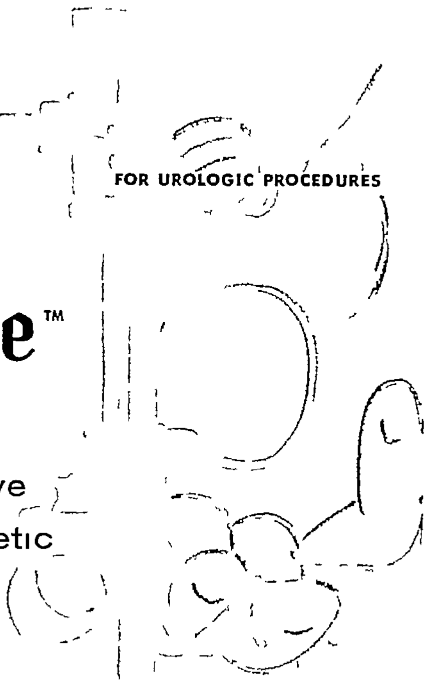

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**DOES WHAT A GOOD TOPICAL ANESTHETIC SHOULD DO**

- quickly produces a potent anesthesia of mucous membranes
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Dyclone Solution for instillation into the urethra and bladder is available in 1 and 8 oz. bottles.

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Reference: Fisher, H. E.: Evaluation of Dyclonine HCl in Minor Urologic Techniques, Missouri Med. 52: 943, 19[illegible]

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